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TUMORS OF THE CERVICAL PORTION OF THE SPINAL CORD

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Tumors of the spinal cord occupy a prominent position in the field of neurologic diagnosis and neurosurgery. Their early recognition is of importance, for long-continued pressure frequently leads to irreparable damage to the spinal cord, which cannot be altered by removal of the tumor. When situated in the cervical portion of the spinal cord these tumors produce more bizarre symptoms than when they are in the thoracic, lumbar or sacral regions and are likely to be confused with other clinical conditions for which operation is not so imperative or so successful. Although tumors occur less frequently in the cervical region than in other portions of the spinal cord, there were 91 tumors of this region in a series of 597 pathologically verified tumors of the spinal cord at the Mayo Clinic.

In presenting the results of surgical, clinical and pathologic observation of tumors in the cervical region, the 91 cases have been reviewed and found to be representative of the various types of lesions that occur in this region.

There were 22 extradural tumors; of these, 12 were neurofibromas, 6 were protruded intervertebral disks (chondromas), 2 were chordomas, 1 was a tuberculoma and 1 was a granuloma (Hodgkin's type). Six tumors proved to be both intradural and extradural and were neurofibrous, of the so-called dumbbell type.

Forty-four intradural, extramedullary tumors comprised the largest group and included 1 angiomatous varix, 2 hemangioendotheliomas, 4 hemangiomas, 16 neurofibromas and 21 meningiomas. The intramedullary group contained 19 tumors, of which the greater majority were identified histologically. They represented the gliomas, and Kernohan has demonstrated that they range from spongioblastoma multiforme through the astrocytomas to the ependymomas. In some of

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the cases in which cystic degeneration had taken place, it was thought surgically inadvisable to attempt removal of tissue after aspirating the cyst.

Such a review of these surgically verified lesions illustrates the relative futility of attempting to predict the type of tumor that exists in any given case on the basis of either the age of the patient or the duration of the symptoms. Nevertheless, in considering the various groups of tumors certain generalizations may be made which should prove to be of diagnostic value.

The 21 meningiomas were removed from patients who ranged in age from 29 to 59 years. It is noteworthy that only 3 of the 21 patients were less than 35. Meningiomas occurred at all levels in the cervical region, but were more frequent in the upper portion. Fourteen of the 21 tumors were situated in the region corresponding to the upper four cervical segments.

The neurofibromas comprised a slightly larger group, there being 34 such tumors in this series. The ages of the patients ranged from 12 to 67 years, but there was a definite tendency for the tumors to occur among young persons. Seventeen of the 34 patients were less than 35. Neurofibromas likewise occurred at all levels of the cervical region, but it is significant that 19 of the 34 tumors arose from the fourth, fifth and sixth cervical nerve roots. The relation of these tumors to the dura mater is of interest. Sixteen tumors were intradural; 6 were both intradural and extradural, and 12 were extradural. There were 9 of the extradural lesions which had extended laterally through the intervertebral foramen and had formed true dumbbell tumors.

Intramedullary growths included 19 tumors of varying histologic character. Patients with these tumors varied in age from 8 to 52 years, but, contrary to most opinions, intramedullary growths were not more common among young persons than they were among the older ones, nor did the clinical course tend to be short and rapid. Only 9 of the 19 tumors occurred before the age of 35. These tumors generally involved a large portion of the cervical region of the cord, and it was often impossible to state the exact extent of the lesion. The upper limit of the tumor in 14 of the 19 cases reached as high as the upper four cervical segments.

The 10 extradural lesions consisted of 6 protruded intervertebral disks, 2 chordomas, 1 tuberculoma and 1 granuloma (Hodgkin's type). The only significant feature of this group was the occurrence of a protrusion of the sixth intervertebral disk in 5 cases and of the fifth intervertebral disk in 1 case.

The group of vascular lesions consisted of 4 hemangiomas, 2 hemangioendotheliomas and 1 angiomatous varix. These lesions were all intradural and showed no distinctive features with respect to the age of the patient or the level of the lesion.

SYMPTOMS AND SIGNS

The duration of symptoms produced by the various tumors of the spinal cord in this series is in distinct contrast to that of analogous lesions that affect the brain. Intracranial meningiomas are notoriously slow in development and may not cause symptoms for many years, but when a meningioma is situated intraspinally the duration of symptoms is short. Seventeen of 21 cervical meningiomas had given symptoms for three years or less. On the other hand, intramedullary tumors, which would be expected to have a rapid onset of symptoms, often resulted in the longest clinical course. The duration of symptoms in 9 of the 19 cases of intramedullary tumors was five years or longer. In 1 case a history of eight years was obtained, in 2 a history of ten years and in 1 a history of thirteen years. Thus, the course of intramedullary lesions of the spinal cord is at variance with the usual rapid course of intracerebral lesions.

The duration of symptoms produced by neurofibromas was longer, on the average, than that produced by the meningiomas. Only 18 of the 34 neurofibromas produced symptoms for three years or less.

The first symptom experienced by 63 of the 91 patients in this series was pain. The neck was the most common site of the pain, and all but 5 of the 63 patients had pain referred to the neck, shoulders or arm. It is of interest that 76 per cent of the patients with intramedullary tumor and all of the patients with vascular lesions complained of pain as the initial symptom. Neurofibromas, developing as they do from nerve roots, would be expected to produce pain as an initial symptom more frequently than other intraspinal tumors; however, in this series, only 61 per cent of the 34 patients who had neurofibromas indicated that pain was the initial symptom, whereas 71 per cent of the patients with meningioma had pain as the first symptom. The lower frequency of pain associated with neurofibromas might be accounted for by the development of such tumors from the anterior nerve roots in a number of cases; however, this seems improbable when it is considered that motor weakness was the initial symptom of only 6 of the entire series of 91 patients.

The initial sensory disturbance was generally in the form of paresthesias or subjective numbness. As would be expected, the upper extremities were involved first in the majority of cases, and most frequently one hand alone was the site of the initial disturbance. Important in this respect is the fact that in 22 cases (24 per cent) sensory involvement occurred first in the lower extremities. One leg alone was affected in 10 cases, and both legs were involved in 12 cases. One patient complained of a severe sensation of burning in both feet for a long period prior to the development of subsequent symptoms.

The first motor symptoms were referred to the upper extremity in 52 per cent of the cases, in which extension of the pain to one hand and arm was the most common type of onset. The fact warrants emphasis that in 35 of the 91 cases motor disturbance was first noted in the legs and feet. Noteworthy in this respect were the cases of neurofibroma, because in more than half this group early weakness in the lower extremities was observed.

Pain is one of the most consistent features of tumors of the spinal cord. Ninety-three per cent of the patients in this series suffered pain of the so-called root type at some time during the course of their illness. The distinctive feature of this symptom is the increased intensity of the pain that occurs when the patient coughs, sneezes or strains. The pain usually is not diffuse, and during the early stages tends to recur in one restricted region. Pain at night, especially during the early morning hours, is common and appears to have a direct relation to the degree of pressure of the cerebrospinal fluid. It is frequent and almost a pathognomonic feature of root pain that it awakens the patient from a sound sleep and that he is not relieved except by sitting or walking. The exact mechanism of this clinical feature is not clearly understood. The pain is usually recurrent and tends to become more severe as time passes, but seldom presents the sudden severe onset so frequently noted with tumors that involve the cauda equina. At some time, pain was associated with every meningioma, intramedullary tumor and vascular lesion. Only 6 patients of the entire series were without pain; 3 of these had an extradural lesion, and, curiously, 3 had a neurofibroma.

Extensive weakness was the rule in this group of patients by the time that they presented themselves for treatment. Quadriplegia of some degree was observed in 41 patients; 9 patients had weakness involving three extremities, and 9 had definite hemiplegia. Twenty patients had paraplegia of both arms with normal motor power in the legs. It is important from a diagnostic viewpoint to note that in 10 per cent of the total group motor weakness was confined to the lower extremities, with normal power in both arms. Motor weakness of this type, especially in the occasional cases in which it is not associated with any objective loss of sensation, may lead to erroneous localization of the lesion at a low level unless adequate attention is paid to the site of the root pain in the cervical distribution of nerves.

Intramedullary lesions again gave results somewhat contrary to the general rule. In only 8 of the 19 cases in this group was there extensive weakness, and in 52 per cent weakness was limited to the upper extremities. In this series there were only 3 cases in which motor disturbance could not be demonstrated.

Atrophy of the muscles of the arm or hand was observed in 22 cases and, as one might expect, was most commonly associated with tumors

affecting the four lowest cervical segments. Muscular atrophy associated with fibrillary twitching was noted in 21 cases. Thus, in 43, or nearly one half, of the cases either atrophy alone or atrophy plus fibrillary twitchings was present. This was most commonly associated with the intramedullary lesions (in 63 per cent of cases), as compared with its occurrence in 38 per cent of cases of meningioma and in 40 per cent of cases of neurofibroma.

A distinctive feature of tumors of the cervical region of the cord is the great variability in the objective sensory disturbances. Definite loss of sensation could be demonstrated in only 67 cases, and in only 56 per cent of this number was there a well defined sensory level. There were 9 cases in which anesthesia could not be demonstrated.

The presence of a dissociated type of anesthesia is considered by many to be substantial evidence in favor of an intramedullary lesion. However, in 51 of the 67 cases in our series in which there were definite sensory changes pain, touch and temperature sensibilities were impaired to an unequal extent. The frequency of this type of sensory disturbance was substantially the same in all groups of cases that comprise this series. Well advanced lesions produce great impairment of all forms of sensation, but in the early stages of compression of the cervical region of the cord sensations of pain and temperature tend to be far more affected than tactile sensation. The exact mode of production of dissociated anesthesia, especially in cases of extramedullary lesions, is not definitely understood. Probably, as Foerster has mentioned, sensations of pain and temperature are subserved by only one pathway, whereas the tactile sensation ascends through both the anterolateral and the posterior columns. Otherwise, it would be difficult to understand why pain, which is phylogenetically the oldest sensation, should be so readily impaired whereas tactile sensibility is preserved. A case might be mentioned which further illustrates the difficulty of determining the method of production of signs and symptoms. A large meningioma, presenting exactly in the midline posteriorly, by causing severe compression of the cord had not produced any alteration in joint or vibration sensibility even though the posterior columns could not have escaped injury.

It should be mentioned, as a word of warning, that occasionally a tumor of the cervical region of the cord will produce a sharp sensory level, even as low as the middorsal region.

In 68 cases complete studies of the cerebrospinal fluid were made after lumbar puncture. In 19 cases lumbar puncture was not performed, and in the remaining 4 cases studies of cerebrospinal fluid were carried out before the advent of routine determinations of the total protein. In 67 of the 68 cases either an increased total protein content of the cerebrospinal fluid or evidence of partial or complete subarachnoid block was revealed. In 30 of these cases both were present. The only case in

which such changes were not found was that of an unusual neurofibroma that had embedded itself completely in the substance of the spinal cord. This peculiar tumor acted as an infiltrating glioma, and it could not be separated totally from the cord at the time of operation. It cannot be stated that the presence of abnormalities of the cerebrospinal fluid establishes the diagnosis of a tumor, but their absence can be said almost certainly to exclude the presence of a neoplasm in the cervical portion of the spinal cord.

Cytologic studies of the cerebrospinal fluid removed in these 68 cases revealed more than 12 cells per cubic millimeter in only 4 cases. The highest value obtained in 1 case was 23 cells per cubic millimeter.

Emphasis should be placed on the value of a careful sensory examination after lumbar puncture. Not infrequently decided progression in anesthesia will be observed, even subsequent to removal of small amounts of cerebrospinal fluid. Occasionally a definite sensory level will appear, which may prove invaluable in localization.

Study of roentgenograms of the cervical region of the spine proved to be of less localizing value than is generally true of such a procedure for other portions of the vertebral column. Roentgenologic evidence of erosion of the pedicle and widening of the spinal canal was obtained frequently, but the most consistent finding was enlargement of the intervertebral foramena associated with neurofibromas of the dumbbell type. It is of interest to note that hyperostosis of the vertebrae was not associated with an underlying meningioma in any case. The explanation of this is not clear, but it might be accounted for by the absence of diploic channels in the overlying bone and by the peculiar separation of the dura into two layers within the vertebral canal. The intervening fat-filled epidural space may prevent excessive vascularization and invasion of the bone.

Stiffness of the neck, although a frequent observation, was not of definite diagnostic value. Horner's syndrome commonly is considered as frequently associated with tumors of the cervical portion of the spinal cord. However, in this series it was neither a common finding nor one of any localizing significance.

DIFFERENTIAL DIAGNOSIS AND SURGICAL TREATMENT

A history of root pain, gradual, progressive impairment of motor and sensory function, positive roentgenographic findings and abnormalities of the cerebrospinal fluid are definitely suggestive of compression of the spinal cord, which is nearly always caused by an intraspinal neoplasm. Clinical experience has demonstrated the extreme difficulty in establishing an accurate preoperative pathologic diagnosis; however, there are factors in each case that lead one to suspect a particular type of lesion.

Rapid onset of symptoms is suggestive of either a primary or a metastatic malignant tumor. Primary lesions of the vertebrae, or secondary bony changes from extrinsic processes generally, can be recognized from the evidence of erosion, destruction or proliferation of bone as detected in the roentgenograms of the vertebral column. Vascular tumors, either hemangiomas or hemangioendotheliomas, seldom present any clinical features which are sufficiently characteristic to warrant a preoperative diagnosis.

The more common inflammatory and degenerative lesions of the spinal cord generally offer little difficulty in diagnosis, provided that careful neurologic examinations and study of the cerebrospinal fluid are carried out. However, pachymeningitis cervicalis hypertrophica and syringomyelia can simulate so closely the signs and symptoms of tumor that operation in such cases may be performed with the mistaken diagnosis of a tumor of the spinal cord. They may produce not only neuralgic pain throughout the cervical distribution of nerves but also muscular atrophy of the small muscles of the hands, with fibrillation, and even evidence of blockage of the subarachnoid space. Metastatic abscess of the spinal cord may produce compression, but the history, febrile course and systemic reaction leave little doubt as to the nature of the lesion.

The two conditions which offer the greatest difficulty in diagnosis are chronic cystic arachnoiditis and multiple sclerosis. The former may present all the signs and symptoms of a tumor of the spinal cord, but seldom is there the usual history of steady progression. In addition, examination of the cerebrospinal fluid almost never reveals an increased amount of total protein or evidence of subarachnoid block, so characteristic of tumor. Multiple sclerosis generally offers little difficulty in diagnosis, but in its atypical forms it may closely simulate a tumor. Again, examination of the cerebrospinal fluid is of distinct value, particularly if a colloidal gold curve of the zone 1 type is present. Remissions so common in multiple sclerosis may be simulated by tumors of the cervical region of the cord, but in cases of the latter it will be noted that, although the fluctuations may be striking, there is never a return to normal.

The surgical approach employed in the removal of tumors from the cervical region of the spinal cord should differ from that employed in performing the usual laminectomy. The extreme degree of mobility of the cervical portion of the vertebral column, combined with the absence of strong bony and muscular support in the dorsal and lumbar regions, makes the usual bilateral laminectomy a somewhat hazardous procedure. A hemilaminectomy, leaving intact the spinous processes with their ligamentous attachments, is the method of choice and affords adequate exposure without the risk of subsequent dislocation of the cervical

vertebrae (fig. 1). The side on which the hemilaminectomy is to be done is determined by the side on which the muscular weakness first developed. At operation, the tumor was observed on the side corresponding to the arm or leg in which motor weakness was first noted in 90 of the 91 cases.

The use of iodized poppyseed oil in the localization of a tumor of the spinal cord has proved to be of much less diagnostic value in the cervical region than in other portions of the spinal canal. The side on which the lesion is situated cannot be ascertained with any greater frequency by use of the iodized oil than by the clinical findings alone.

The choice of anesthesia depends on the age and condition of the patient, as well as on the position of the patient on the operating table. Local infiltration anesthesia should be used whenever general anesthesia seems to be contraindicated. However, since we have adopted the upright

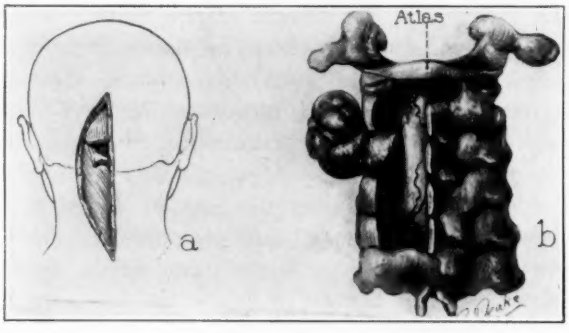

Fig. 1.—Drawings showing (*a*) cutaneous incision and (*b*) exposure with hemilaminectomy.

position for cerebellar and cervical operations we have found that the use of the intratracheal tube combined with administration of ether by the drop method is the most satisfactory method of providing anesthesia.

Introduction and insertion of the intratracheal tube are carried out in the anesthesia room with the patient placed in the prone position on a cart. The patient is then wheeled into the operating room and is lifted into the upright position on the seat affixed to the operating table. Then a midline incision is made, extending upward over the occipital region if the lesion is situated in the cervical region, through which a hemilaminectomy is done.

It is possible for the exact level of the lesion to be established roentgenologically in some cases by use of iodized oil, but hemilaminectomy, begun in the midcervical region and continued up or down as the findings indicate, is equally effective (fig. 2). Furthermore,

direct exploration eliminates the necessity of leaving an irritating foreign body in the subarachnoid space. This is not a condemnation of iodized poppyseed oil but a warning against its indiscriminate use, which should be avoided unless the benefits to be derived more than justify the risk of transient meningeal irritation.

The ease with which surgical removal of the tumor is accomplished depends more on the relation of the growth to the spinal cord than on the histologic character of the lesion. From the standpoint of the subsequent return of function, the degree of compression of the spinal cord is not nearly so important as the duration of the local pressure. No doubt this feature can be explained adequately on a vascular basis; that is, the

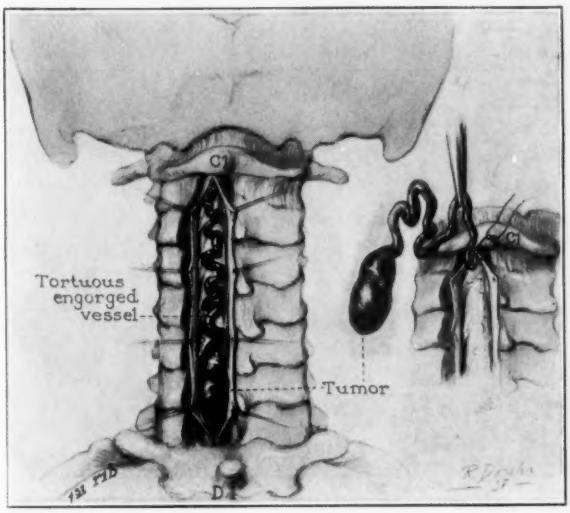

Fig. 2.—Cervical hemilaminectomy for the removal of an extensive vascular attachment of a hemangioma.

longer the pressure the more permanent the vascular changes. Tumors situated on the dorsal aspect of the spinal cord present less technical difficulty in removal from an anatomic standpoint than do those that arise anterior to the dentate ligament.

Neurofibromas usually appear as small isolated tumors arising from a single nerve root, generally the sensory portion, and as a rule can be removed totally by resection of the involved portion of the root. Occasionally, the lesion is more extensive and becomes fusiform, with peripheral extension to or through the intervertebral foramen. Dumbbell tumors present not only the usual intraspinal lesion but also an extraspinal extension through the intervertebral foramen. The portion of the tumor within the neck may attain tremendous size. Occasionally

tumors are encountered which have taken origin from multiple nerve roots, and in each instance such a lesion requires individual alterations in the surgical attack.

Meningiomas present a more difficult problem because of their dural attachment and great vascularity (fig. 3). Frequently, the *en plaque* type is encountered on the dorsal portion of the dura; this form lends itself to ready total removal merely by wide resection of the involved dura. Likewise, easy removal may be accomplished for that type of polypoid or pedunculated growth which exhibits a limited dural attachment. More difficult to resect are the lesions that lie anterior to the cord and that involve the dura extensively. Attempts to resect this type of meningioma intact may lead to irreparable damage to the spinal cord itself; it is best removed piecemeal. Adequate exposure for this

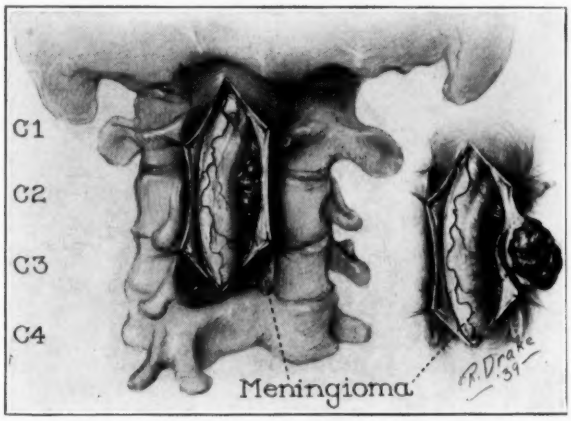

Fig. 3.—Removal of a meningioma by means of hemilaminectomy.

procedure may be had by resection of one or more posterior roots, section of the dentate ligament and gentle rotation of the spinal cord. Resection of the posterior sensory roots will leave so small an area of permanent sensory loss as to be of minimal importance. Additional exposure can be obtained easily by lateral incision of the dura made at right angles to the long axis of the vertebral column. A misleading, and not infrequent, observation is the presence of cystic arachnoiditis with large collections of fluid either immediately above or below an intradural, extramedullary tumor. No doubt in the past, before this fact was recognized, many tumors of the spinal cord have been overlooked and a diagnosis of chronic cystic arachnoiditis has been made.

Extradural compression of the spinal cord may result from many lesions other than a protruded intervertebral disk, and in this series of cases neurofibromas, chordomas, tuberculomas and granulomas were

causative agents. Removal of a protruded intervertebral disk, provided that it presents laterally, is less complicated from a technical standpoint than is the removal of a primary intraspinal tumor. Troublesome bleeding may occur from the epidural venous plexus, but this is rarely serious and can be controlled with transplants of muscle tissue. The approach is entirely extradural, and once the protruded lump has been located and the overlying nerve roots have been carefully retracted, a cruciate incision is made in the posterior longitudinal ligament and the cartilaginous mass is easily removed. Protrusions in the midline in the cervical region present a more delicate problem, and occasionally it is better to resort merely to decompression of the spinal cord than to hazard the risk of probable damage to the cord.

Intramedullary lesions, although comprising only 20 per cent or less of tumors of the cord, afforded by far the most difficult surgical problem. Grossly, these tumors produce a fusiform enlargement of the cord that extends over several segments, and usually presents an increased local vascularity. Inspection of the cord affords little evidence of the exact nature of the underlying pathologic lesion, which may prove to be any one of the primary gliomas that affect the central nervous system, or, as not infrequently occurs, a degenerative, cystic or hemorrhagic process, such as is seen in cases of syringomyelia and hematomyelia. On occasion, the dura overlying an intramedullary tumor may be the site of a chronic inflammatory reaction. This results in thickening and discoloration of the dura, which becomes adherent to the spinal cord. Extreme care and general dissection are necessary to separate the dura from the medullary substance and to prevent operative trauma to the latter.

Of all surgical problems concerned with the spinal cord, there is probably no decision more difficult to make than that which regards the proper surgical management in each case in which the gross picture of an intramedullary tumor is presented. Aspiration of material from the interior of the spinal cord with a fine needle introduced in the midline posteriorly often is the diagnostic procedure of choice, but this must be done carefully to avoid trauma to the medullary substance. If a tumor is encountered on diagnostic puncture or is suspected on clinical grounds alone, removal is best accomplished through a posterior midline incision made in an avascular region. Successful enucleation of large, intramedullary lesions, such as the ependymoma removed in case 3 of our series, may be accomplished if extreme care is exercised in manipulation of the delicate tissues. The essence of all successful surgical treatment of the spinal cord lies in judicious and careful handling of tissue combined with meticulous hemostasis.

The anatomic characteristics of the cervical portion of the spinal cord are such that variations of only a segment or two in the situation

of the lesion may markedly alter the clinical picture. For the purpose of study the cases have been grouped according to the level at which the tumor was situated at the time of operation.

REPORT OF CASES

CASE 1.—A woman aged 53 came to the Mayo Clinic complaining of pain in the left side of the neck and weakness and numbness of the left arm and leg. Two years prior to examination she first noted pain at night, which often required morphine for relief. The pain, which at times extended down the left arm to the elbow, was intensified by coughing or sneezing. Four months after the onset

Fig. 4.—Roentgenologic evidence of enlargement of the intervertebral foramen of the cervical vertebrae, which allowed localization of the tumor.

of pain, numbness and weakness were first noted in the fourth and fifth fingers of the left hand; they progressed gradually in extent until the entire left side of the body was affected.

The patient walked with a definitely spastic gait, and the neck was held in a rigid position. A firm, fixed nodule was present high in the posterior cervical triangle on the left side.

Neurologic examination revealed moderate weakness of the left side, with marked spasticity. Sensory tests failed to reveal a sensory level, although there was a dissonated type of anesthesia. Lumbar puncture revealed evidence of complete subarachnoid block. Examination of the cerebrospinal fluid disclosed a total protein content of 40 mg. per hundred cubic centimeters. Roentgenologic examination of the cervical portion of the spine revealed erosion of the pedicles and posterior portion of the bodies of the second and third cervical vertebrae (fig. 4).

Left cervical hemilaminectomy revealed a large extradural tumor extending laterally through the intervertebral foramen between the second and the third cervical vertebra. A large neurofibroma of dumbbell type, which measured 5 by 2 by 1 cm., and a massive extravertebral portion were removed (fig. 5). Convalescence was uneventful.

This case is of particular interest from the standpoint of pain as an early symptom of a tumor of the cervical portion of the spinal cord. Pain was present for approximately twenty-two months before any further neurologic involvement was evident.

The paucity of neurologic signs in the presence of such a large tumor probably can be explained by the more rapid growth of the extraspinal portion of the tumor, with extension into the posterior cervical triangle rather than into the rigid spinal canal.

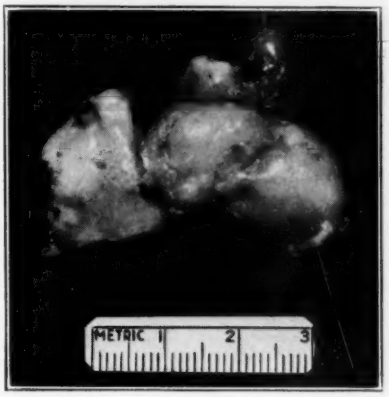

Fig. 5.—Tumor after removal, showing both the extravertebral and the intravertebral portion.

CASE 2.—A man aged 35 had been well until eight months prior to admission, when he noted constant pain in the neck, which extended into the shoulders. Pain was noted in the right hand and was soon followed by weakness and incoordination. Three months later there were weakness and paresthesia of both lower extremities.

Roentgenologic examination of the cervical portion of the spine disclosed evidence of destruction of the right side of the fourth and fifth cervical vertebrae. Neurologic examination revealed marked weakness of the right arm and milder weakness in the left arm and both legs. There were definite atrophy and visible fibrillary twitching of the muscles of the right arm. The biceps reflex was absent in both arms, but the triceps reflex was exaggerated. The Hoffmann sign was elicited on the right side. There was a dissociated type of anesthesia of both arms and of the left leg. Tactile sensation was present, but pain and temperature sensibility was greatly impaired.

A right hemilaminectomy of the fourth, fifth, sixth and part of the seventh cervical vertebrae revealed a large vascular tumor on the right side, anterior to the dentate ligament; it had compressed the cord to a tenth of its normal size. The tumor was totally removed and proved to be a meningioma. The patient had an uneventful convalescence and six months after dismissal was working daily.

This case is interesting because there was a history of less than eight months, with only minimal motor weakness, and yet, at the time of operation, extreme compression of the spinal cord was observed.

CASE 3.—A man aged 40 came to the clinic because of weakness and numbness of the arms, of four years' duration, and of the legs, of three years' duration. Numbness was noted first in the right hand, but it gradually involved the entire arm. A year later there were numbness of the left hand and arm and slight weakness of the left shoulder.

Neurologic examination disclosed marked weakness of both upper extremities, with muscular atrophy of both shoulders, most marked on the right side.

There were fibrillary twitchings in both biceps muscles. Anesthesia of the dissociated type, most marked for pain and temperature sensibility, was present below the level of the clavicles and involved the upper extremities more than the lower.

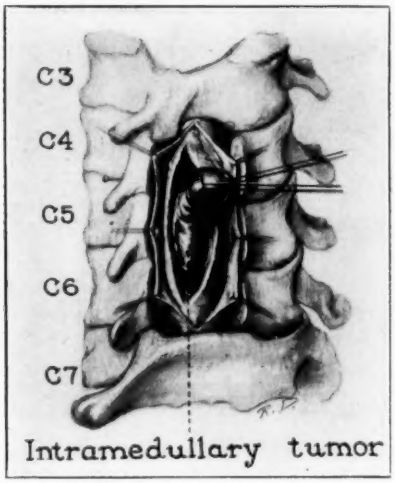

Fig. 6.—Intramedullary tumor, which was totally removed.

The biceps reflex was absent on both sides, and the triceps reflex was absent on the right side. The Hoffmann sign was elicited bilaterally. Lumbar puncture revealed evidence of partial subarachnoid block, and examination of the cerebrospinal fluid disclosed 80 mg. of total protein per hundred cubic centimeters.

Right hemilaminectomy of the fourth, fifth and sixth cervical vertebrae revealed a fusiform enlargement of the spinal cord. This was incised on the dorsal aspect in the midline, and a large, encapsulated, granular, intramedullary tumor, which measured 9 by 2 by 1.5 cm., was removed; it weighed 26 Gm. and proved histologically to be an ependymoma (fig. 6). Convalescence was uneventful, and at the time of dismissal the patient was able to walk without assistance.

This case illustrates the similarity in neurologic signs and symptoms produced by intramedullary and by extramedullary tumors of the cervical region of the cord, which makes accurate localization impossible on the basis of the usual clinical methods alone.

The successful removal of the tumor from within the substance of the spinal cord in this case emphasizes the fact that the mere presence of an intramedullary lesion does not necessarily preclude the possibility of surgical removal of the tumor.

CASE 4.—A girl aged 16 years came to the clinic because of progressive weakness of both legs, which had been present for five months. She noted definite weakness and incoordination in both legs and soon afterward in the left arm. The weakness was progressive, and within a month she was unable to talk. She had not noted any subjective sensory disturbance.

Neurologic examination demonstrated marked quadriplegia. There was a definite sensory level, which corresponded to the first dorsal segment. There was some atrophy of the small muscles of both hands. The biceps reflex was exaggerated on both sides.

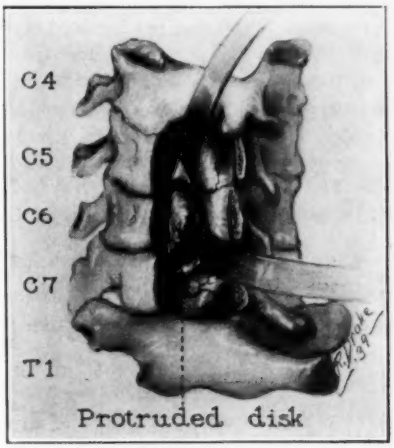

Fig. 7.—Protruded intervertebral disk.

Roentgenologic examination of the cervical portion of the spine disclosed a calcified tumor within the spinal canal on the left side, at the level of the seventh cervical vertebra. Lumbar puncture disclosed a complete subarachnoid block, and examination of the cerebrospinal fluid revealed a total protein content of 360 mg. per hundred cubic centimeters.

Left hemilaminectomy of the fifth, sixth and seventh cervical vertebrae revealed a large extradural tumor, which had compressed the spinal cord to about a fifth of its normal size. The tumor was removed completely and proved to be a protruded intervertebral disk (fig. 7). The patient was able to walk when she left the hospital, twenty-two days after the operation.

The case of this patient, the youngest in our series, is of great interest because of the similarity of the history and clinical findings to those of primary tumors of the spinal cord and meninges. This case represents a typical posterior protrusion of an intervertebral disk into the spinal canal. Such lesions are less common in the cervical than in the lumbar

region, but when present tend to produce more severe neurologic manifestations because they compress the spinal cord itself rather than the cauda equina and lumbar nerve roots.

CASE 5.—A man aged 28 came to the clinic because of weakness of the legs and difficulty in walking, of two years' duration. The weakness was gradually progressive until six months before registration, when he was able to walk only a few yards without resting. At that time he noted that both arms became tired easily. He had difficulty in starting the urinary stream. There was no pain in the neck or thorax.

General examination gave essentially normal results. Neurologic examination disclosed paralysis of both legs, with the more marked weakness on the right side. An area of anesthesia was present over the lower portion of the thorax and the upper part of the abdomen on the right side. The tendon reflexes in both legs were exaggerated.

Subarachnoid block was not present, and examination of the cerebrospinal fluid disclosed a total protein content of 400 mg. per hundred cubic centimeters. Roentgenologic examination of the cervical portion of the spine revealed evidence of erosion of the pedicles of the sixth and seventh cervical vertebrae.

Studies with iodized poppyseed oil revealed a lesion opposite the seventh cervical interspace. Right cervical hemilaminectomy revealed a large intradural and extradural neurofibroma, measuring 4 by 2 by 2 cm., which had extended through the intervertebral foramen. The tumor was totally removed. Convalescence was uneventful; at dismissal the patient was able to walk well without assistance.

It is unusual to have a two year history of progressive weakness of both legs produced by a tumor of the cervical portion of the cord without any evidence of involvement of the arms.

SUMMARY

In a study of 91 surgically verified cases of tumor of the cervical region of the spinal cord it has been found that pain in the neck is the outstanding early symptom. Muscular weakness usually begins in the arms but may involve the legs, is progressive and is usually the patient's chief complaint. Dissociation of anesthesia is a constant accompaniment of all types of lesions of the cervical portion of the cord, but is not in itself diagnostic of any one type of condition.

Lumbar puncture with careful manometric studies and complete examination of the cerebrospinal fluid are of great diagnostic value. Abnormal findings in one or both tests are almost constantly associated with neoplasms that involve the cervical portion of the spinal cord. Sphincteric disturbances of variable degrees were present in many cases, but were not of diagnostic or localizing value. Surgical management of tumors of the spinal cord consists of hemilaminectomy on the side of the tumor. This gives adequate exposure without sacrificing the stability of the vertebral column.

ACUTE ASCENDING PARALYSIS (LANDRY'S PARALYSIS)

A CLINICOPATHOLOGIC STUDY

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Acute ascending paralysis was first described as a disease entity by Landry,[1] in 1859. Further experience, however, has shown that it is in reality a syndrome which may have many causes and may appear under many guises. A diagnosis of acute ascending (Landry's) paralysis, therefore, has come to mean little unless at the same time some statement can be made concerning its cause. It is to stress these features of acute ascending paralysis, as well as to discuss the obscure problem of its pathologic background, that we report 9 cases which we have personally observed.

REPORT OF CASES

In most cases acute ascending paralysis is fatal. The following 5 cases illustrate the fatal type of this syndrome.

CASE 1.—*Acute ascending paralysis, preceded by an attack of grip. Flaccid paralysis of all limbs, with loss of reflexes, no fibrillations and no sensory disturbances. Slight pleocytosis of the spinal fluid. Death from medullary involvement. No autopsy.*

History.—L. B., a male nurse aged 27, entered the Pennsylvania Hospital on Dec. 4, 1934, in the service of Dr. David L. Farley, with the story that he began to feel "grippy" with aching in the muscles, loss of appetite and malaise about Thanksgiving Day, 1934. He went to bed, but his symptoms did not subside. About ten days later he experienced pain in the epigastrium and right upper quadrant and vomited. On admission to the hospital he complained of burning pain in the epigastrium.

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1. Landry, J. B. O.: Note sur la paralysie ascendante aiguë, Gaz. hebd. de méd. et de chir. **6**:473, 1859.

Examination and Course.—Physical examination on admission gave normal results. The temperature, pulse rate, blood pressure and white cell count were normal. Vomiting continued, and the abdominal pain was supplemented by pain in the back and legs.

Clinical Data in Nine Ca

Case; Sex; Age, Yr.	Etiologic Factors	Duration of Prodomal Symptoms	Mode of Onset	Fever	Systemic Reactions	Initial Paralyses	Subsequent Order of Paralyses	Muscle Tone	Muscle Atrophy	Tendon Reflexes
1 M 27	.....	10 days	.....	None	Malaise; vomiting; pain in right upper quadrant	Legs	Arms, face, thoracic and abdominal muscles, muscles of swallowing and respiration	Hypotonia	No fibrillations or atrophies	Abolished except ankle jerk
2 F 41	History of purulent peritonitis	8 weeks	.....	None	Malaise	Legs and arms	Respiratory muscles	Hypotonia	.....	Abolished
3 M 43	History of exposure to lead	55 days	.....	None on admission	Pain and numbness	Feet	Legs, thighs, hands, forearms, arms	Hypotonia	None	.....
4 F 25	.....	.....	.....	Slight, 99-100 F.	Abdominal pain	Proximal portions of limbs	Trunk, shoulders, hands, biceps and triceps; muscles of swallowing	Hypotonia	.....	Only right ankle jerk obtained
5 M 23	.....	5 days	.....	None, except at death	None	Legs	Legs, arms, trunk	Hypotonia	None	Abolished
6 M 35	.....	2 days	.....	None	.....	Legs	Legs, arms, trunk, neck	Hypotonia	Marked	Biceps, triceps and patellar reflexes diminished; ankle jerk absent
7 F 42	.....	Several weeks	.....	None, except with respiratory infection	Feeling "poorly"	Legs	Arms, trunk, intercostal muscles, muscles of swallowing	Hypotonia	None	Abolished
8 M 33	Respiratory infection	.....	.....	None	None	Weakness of left leg	All limbs within 48 hours, trunk and abdominal muscles	Hypotonia	None	Abolished
9 M 60	Colds	About 6 days	Gradual	At onset	General malaise	Weakness of legs	Legs, arms, trunk	Hypotonia	Quadriceps and hamstring muscles	Abolished

Neurologic examination, about two weeks after admission, disclosed marked weakness of the legs and less marked weakness of the arms. The biceps and triceps reflexes were absent; the patellar reflexes were decreased, and the ankle jerks were very active. There were no muscle atrophies or fibrillations; no sensory changes and no tenderness of the nerve trunks; some tenderness was present over the lumbar vertebral spines. The cranial nerves were normal except for a habitual blankness of expression. Three days later there was much more severe weakness of all the extremities, and the muscles were toneless. No fibrillations were seen. All the tendon reflexes were now abolished, except for a slight

ankle jerk on the left. The abdominal reflexes were absent. There were no sensory disturbances. On the following day the patient was placed in a respirator because of difficulty in breathing, due to complete paralysis of the thoracic and abdominal muscles. A few days later facial diplegia developed. This was soon

of Acute Ascending Paralysis

Abdominal Reflexes	Sphincter Disturbances	Spontaneous Pain	Nerve Tenderness	Anesthesia	Laboratory Data	Duration of Disease	Outcome	Cause of Death	Pathologic Observations
Absent	Late in disease	Epigastrium	None	None	White blood cells 6,000 and 25,200; cells of cerebrospinal fluid, 50 to 15; Wassermann reaction of fluid negative	44 days	Death	Respiratory failure	No autopsy
Absent	None	.....	.....	Patchy hypalgesia	Albuminuria; four cells in spinal fluid; Wassermann reaction negative	.....	Death	Respiratory failure	Severe changes in ganglion cells in anterior horns and vagal nuclei
Absent	Retention of urine and feces	.....	.....	Loss of sense of position in toes	White blood cells 14,800	4 days	Death	Respiratory failure	Severe changes in anterior horn cells, especially in thoracic and lumbar portions of spinal cord
Absent	None	Muscles	.....	Patchy areas of hypalgesia, coalescing	White blood cells 11,000; cerebrospinal fluid normal	2 weeks	Death	Respiratory failure	
Absent	None	None	None	None	Urine, blood and cerebrospinal fluid normal	12 days	Death		
None	None	None	None	None	Wassermann reactions of blood and fluid negative; colloidal gold curve 4443321000; biopsy of deltoid showed atrophic fibers	3 months	Recovery		
Absent	None	Lower part of back	None	Slight vibratory loss in legs	Normal	3 months	Recovery		
Absent	None	None	None	None	Cells in cerebrospinal fluid 18	1 month	Recovery		
Absent	None	None	None	None	Normal	.....	Partial recovery		

followed by difficulty in swallowing and by some atrophy of the skeletal muscles, without fibrillations. The patient became progressively worse and died on Jan. 7, 1935, about one month after the onset of his illness.

Laboratory Studies.—Repeated urinalyses gave normal results. The leukocyte count of the blood varied from 6,000 to 25,200. The cell count of the spinal fluid on three occasions was 52, 25 and 15 per cubic millimeter; the Wassermann reaction was negative; the colloidal gold curve showed a reading of 0000000000. The spinal fluid contained 85 mg. of sugar per hundred cubic centimeters, and the chloride content on two occasions was 674 and 633 mg., respectively, per hundred cubic centimeters.

This case was clinically a typical instance of acute ascending paralysis, but permission for autopsy was not obtained. No etiologic factor was discovered; the closest approach to any factor of importance was a history of ingestion of canned food on a picnic before the onset of the illness, but no evidence of food poisoning was disclosed. The course of the disease was constantly downward; it was characterized by ever increasing paralysis, with eventually bulbar symptoms and respiratory paralysis. The patient died despite a prolonged stay in the respirator. The case was first regarded as one of hysteria, a diagnosis which is not infrequently made in such instances. The course was afebrile throughout, except for a terminal rise of temperature. There was no laboratory evidence at any time of involvement of the nervous system.

CASE 2.—*Acute ascending paralysis involving all four extremities, with absence of reflexes and of sensory disturbances. Previous history of pus released from posterior colpotomy. Death from respiratory paralysis. Severe changes in ganglion cells of the anterior horns at all levels of the spinal cord and in nuclei of the vagus nerve in the medulla.*

History.—T. B., a Negress aged 41, who entered the Pennsylvania Hospital on Dec. 2, 1935, in the service of Dr. Robert A. Kimbrough Jr., had suffered for weeks with headaches and dull pain in the abdomen and back. The day before admission she coughed a good deal and had a chill. On entrance to the hospital she was found to have tenderness and distention of the abdomen. Five days later the distention was marked. Twelve days after admission a posterior colpotomy was performed and a large quantity of pus released. Later an incision in the right lower abdominal quadrant also released pus. In both instances gram-negative bacilli and Friedländer's bacillus were found. The patient was discharged as improved about seven weeks after admission. She returned to the hospital a week later, complaining of pain in the left upper quadrant and generalized weakness.

Examination.—The left pupil was dilated and irregular and responded sluggishly to light. The lower right side of the face was weak. Complete flaccid paralysis of all four extremities was present. No tenderness of the muscles or nerve trunks was observed, and there were no fibrillations. No tendon or abdominal reflexes were obtained. There were at first patchy areas of hypalgesia in the upper portion of the body and later loss of pain and temperature sensibility down to the second thoracic segment. Position and vibratory senses were intact. The patient died five days after entrance to the hospital.

Laboratory Studies.—Urinalysis showed constant albuminuria. The red cell count of the blood varied between 4,300,000 and 4,600,000. Leukocytosis, with a count of 25,000 to 28,000 cells, was present on the first but not on the subsequent admission. The spinal fluid contained 4 cells per cubic millimeter; there was no increase in the globulin content, and the Wassermann reaction was negative.

Histologic Studies.—These were made at all levels of the spinal cord and the base of the brain. The anterior horn cells at all levels of the cord, but more especially in the cervical and lumbosacral regions, showed various degrees of axonal chromatolysis. Practically all the anterior horn cells were affected. They showed marked swelling of the cytoplasm, with swollen eccentric nuclei, peripheral dispersion of the Nissl substance and often complete absence of tigroid matter. The cytoplasm was filled with fat. Some of the anterior horn cells were small

and atrophic. About one third of the anterior horn cells were of this degenerated type. Normal cells were not seen. The white matter of the spinal cord showed scattered areas in which the myelin sheaths were swollen or destroyed. These areas were observed along the dorsal margins of the cord or in the lateral columns. The dorsal nucleus of the vagus nerve showed evidence of severe cell damage. The cells of this nucleus were frayed, vacuolated and devoid of Nissl substance. Similar, but less pronounced, changes were seen in the nucleus ambiguus.

This patient presented a typical picture of ascending paralysis in relation to a previous abdominal and pelvic operation, in which much pus had been released.

CASE 3.—*Gradually developing ascending paralysis of all four limbs, preceded by pain and numbness and followed by involvement of the sphincters and of muscles of deglutition and articulation, terminating in failure of respiration. Severe changes in anterior horn cells at thoracic and lumbar levels; less severe changes in cervical and sacral portions.*

History.—D. M., a man aged 43, a telephone operator, in 1935 experienced mild transient pains in the lower limbs, which did not incapacitate him. About June 1, 1937, after several days of exertion in painting his house, there developed gradually pain, numbness and weakness, which commenced in the feet and in the course of six weeks extended successively to the legs, thighs, hands, forearms, arms, region of the bladder and trunk. About nine weeks later (August 6), there developed difficulty in swallowing and talking, with retention of feces and urine.

Examination.—On admission to the Graduate Hospital, on Aug. 9, 1937, in the service of Dr. J. C. Yaskin, the patient's temperature was 98.2 F., his pulse rate 100 and his respiratory rate 18. He was emaciated and pale and looked acutely ill and toxic, but exhibited no definite somatic abnormalities. He was clear mentally. There were some weakness of the tongue and soft palate and difficulty with articulation and swallowing. No other abnormalities of the cranial nerves were noted. There were complete flaccid paralysis of both upper extremities, marked paresis of both lower extremities, involving equally the proximal and the distal portions, with generalized emaciation but no localized atrophy and no fibrillations. Weakness of the trunk was marked. All the tendon reflexes were completely abolished, and there were no pathologic reflexes. The abdominal reflexes could not be obtained. The anal sphincter was relaxed. There was loss of sense of position in the toes, but no other sensory loss. There were generalized hyperesthesia, tenderness of the feet on pressure and a positive Laségue sign bilaterally, but no evidences of meningeal irritation.

Course.—In spite of supportive treatment, the patient became rapidly weaker. On August 11 the temperature rose to 100 F., the pulse rate to 160 and the respiratory rate to 50. He died on August 12, three days after admission.

Laboratory Studies.—Routine urinalysis and examination of the urine for lead gave negative results. There was no stippling of the red cells. The blood count showed 14,800 leukocytes, but no other significant changes. The chemical constituents of the blood were normal, and the Wassermann reaction was negative. The spinal fluid pressure was very low, but there was no block. Routine study of the spinal fluid gave normal findings.

Histologic Studies.—The anterior horn cells at all levels of the spinal cord showed definite disease. Not all the cells were affected, and not all levels of

the spinal cord were affected similarly. At some levels only a few cells were diseased, while at others practically all the anterior horn cells were affected.

The thoracic and lumbar levels of the spinal cord were more affected than the others. The anterior horn cells in these areas showed either axonal chromatolysis, with typical swollen, fat-filled cytoplasm and an eccentric nucleus, or atrophic changes characterized by slight, shrunken cytoplasm and a small pyknotic nucleus. Stains for fat revealed heavy accumulations in the chromatolytic cells. Similar changes of a lesser degree were observed in the cervical and sacral segments of the spinal cord. Scattered small patches of demyelination were seen in the white matter of the spinal cord. The number of fibers in the anterior horns was uniformly decreased. There was no meningeal vascular reaction.

From a clinical standpoint, the chief interests in this case are the slow development of the ascending paralysis and the presence of pain and later of tenderness of the nerves. The disease in this case resembled more closely severe multiple neuritis than Landry's paralysis. The absence of fibrillations and of any definitely localized atrophy is in marked contrast to the histologic changes observed in the spinal cord. The etiologic factor in this case was undetermined, although there was a history of exposure to lead.

CASE 4.—*Ascending paralysis, developing in about two weeks, with slight fever. Flaccid paralysis of all limbs, with subsequent atrophy. No sensory disturbances. Death from medullary involvement.*

History.—N. T., a Negress aged 25, was admitted to the Pennsylvania Hospital on Nov. 5, 1936, in the service of Dr. Bernard J. Alpers. She stated that she had had a pelvic operation in 1925, but had otherwise been well until five days before admission, when she began to experience abdominal pain, which became continuous. She gave herself many enemas in an attempt to relieve the pain. She had vomited many times. Otherwise her personal and family history were without significance.

Examination.—Physical examination on entrance gave normal results. The temperature varied from 99 to 100 F. Six days after entrance neurologic examination revealed slight irregularity of the pupils and weakness of the proximal portions of the limbs. There was no tenderness of the nerve trunks. Tendon and abdominal reflexes were absent. There was no gross sensory disturbance.

Course.—Eleven days later the weakness had extended greatly. The muscles of the trunk and the shoulder girdle were now weak. The hand grips were weak, and biceps or triceps movements were not present. The hamstring muscles contracted freely; the quadriceps muscles not at all. Eversion, plantar flexion and dorsiflexion of the feet were preserved. The muscles in general were toneless. The right ankle jerk was the only tendon reflex obtained. There were a few patchy areas of hypalgesia. There was slight muscular tenderness, which varied somewhat. Subsequently the patient complained of muscular pain. About two weeks after admission wasting was noted in the quadriceps muscles; tenderness of muscles and nerve trunks was noted, and a quantitative increase in the areas of hypalgesia was observed. About five weeks after admission both arms and hands were completely powerless, and there was hypalgesia to the chin, although swallowing was normal. After six weeks difficulty in swallowing appeared; the jaws and lips were moved only feebly, and the patient died of respiratory failure.

Laboratory Studies.—Repeated examinations of the urine showed many leukocytes. The white blood cell count was 11,000. Examination of the spinal fluid showed 2 cells per cubic millimeter, a negative Wassermann reaction, a colloidal gold curve of 0000000000, 89 mg. of sugar per hundred cubic centimeters, 30 mg. of protein and 690 mg. of chlorides. Lead was not found in the urine. Cultures of the blood and spinal fluid were sterile.

This case is instructive because of the relatively slow development of the ascending paralysis. The completed picture developed during a period of two or more weeks. The final picture was typical in all respects. No etiologic factor was found.

CASE 5.—*Acute ascending paralysis, of undetermined origin. Flaccid paralysis of all limbs with loss of reflexes, unaccompanied by fibrillations or sensory or sphincter disturbances. Sudden death. Myelopathy of the medulla and spinal cord.*

History.—H. T., a man aged 23, had had a psychosis at the age of 16, and since then had not made a satisfactory vocational adjustment. On April 1, 1937, there developed slight weakness of all extremities. The following morning he observed greater weakness in all the limbs, but was able to dress and walked about with difficulty. Two days later marked paralysis of all the limbs developed, and he became bedridden. There was no history of an antecedent infection, gastrointestinal upset or trauma. He was admitted to the Philadelphia General Hospital four days after the onset, in the service of Dr. J. C. Yaskin, complaining of weakness of all the limbs. There was no history of pain or numbness, or disturbances in sphincter function, swallowing or talking.

Examination.—On admission the temperature was 98 F., the pulse rate 96 and the respiratory rate 20. The patient did not appear acutely ill. He was lucid and strikingly free from anxiety about his paralysis. Somatic examination disclosed no significant abnormalities. The cranial nerves were normal. There was no weakness of the muscles of the neck. There was definite trunkal weakness, so that the patient could not turn from side to side. The abdominal reflexes were absent. The intercostal muscles and diaphram were normal. There was flaccid paralysis of all four extremities, except for occasional movements in the thumbs, toes and quadriceps femoris muscles. No fibrillations were noted. All the tendon reflexes were completely abolished, and there were no pathologic reflexes. Superficial and deep sensibility was normal, and there was no tenderness over the nerve trunks.

Course.—The patient's condition remained unchanged until eight days after the onset of his illness, when his temperature and pulse and respiratory rates rose rapidly; he died suddenly on the tenth day of the disease.

Laboratory Studies.—Urinalysis, the blood count and chemical studies of the blood gave normal results. The Wassermann reaction of the blood was negative. The spinal fluid pressure was normal; routine examination of the spinal fluid disclosed no abnormalities.

Histologic Studies.—The brain in this case showed degenerative changes resulting from prolonged circulatory insufficiency. These were most marked in the association areas of the cortex, the vegetative centers and the extrapyramidal system. Superimposed on this process was acute circulatory stasis with resulting ring hemorrhages, most marked in the periventricular gray matter of both the midbrain and the brain stem.

In the medulla and the cervical region of the cord the effects of both the acute and the chronic stasis were most marked. In the cerebral vascular system fibrosis of the media was superimposed on vessels which showed a congenitally weak structure.

The condition in this case was diagnosed as hysteria prior to the patient's entrance to the hospital and even after admission this possibility was considered. The reasons for this impression were the absence of fever, the fact that the patient did not appear toxic and showed no concern about his serious disability and moreover that he was able to manipulate his limbs by the use of the muscles of the shoulder and pelvic girdles. The hypotonia and the absence of reflexes established the diagnosis. Death in this case was dramatic, and was more comparable with death from sudden occlusion of blood vessels in vital centers than with death from a gradually progressive degenerative disease. The etiologic agent in this case is unknown.

It is generally believed that acute ascending paralysis is practically always fatal. Recoveries, however, occur; when they do, the result is striking, almost startling. The following 4 cases are remarkable examples of such recovery.

CASE 6.—*Acute ascending paralysis following a gastrointestinal upset. Flaccid paralysis of all limbs with decreased reflexes. No sensory and no sphincter disturbances. Complete recovery.*

History.—W. S., a white man aged 35, who entered the Philadelphia General Hospital on Aug. 2, 1935, in the service of Dr. Bernard J. Alpers, on July 4, 1935, had attended a picnic, during which he ate frankfurters and canned food and drank a few glasses of beer. He did not become intoxicated or suffer any immediate gastrointestinal disturbances. On July 5 his legs were weak. Previous to this time he had been perfectly well. The weakness steadily increased, and by noon he found he was unable to lift packages weighing 15 pounds (6.8 Gm.). On the following day he walked with the greatest difficulty in the morning, and at noon was unable to walk at all. Four days later he had no power from his neck to his toes.

Examination.—On admission the patient showed pronounced weakness and was unable to raise his head from the pillow. There was no fever. The cervical, epitrochlear and inguinal lymph nodes were enlarged. The cranial nerves were normal. There were marked weakness and atrophy of the muscles of the limbs, trunk and neck. The muscles of the shoulder girdle, hands, trunk and legs seemed most affected. The deltoid, triceps, biceps brachii and forearm muscles were less affected. The muscles were toneless, and there were no fibrillations. The biceps, triceps and patellar reflexes were diminished. The ankle jerks were not obtained. Sensory examination revealed no abnormalities. There were no sphincter disturbances.

Course.—The patient gradually improved and was discharged as well on Oct. 17, 1935. He was reported as completely well in May 1938.

Laboratory Studies.—Urinalysis gave normal results. The leukocyte count of the blood was 7,150; the red cell count was normal. The Wassermann reactions of the blood and spinal fluid were negative. The spinal fluid contained no cells,

but the colloidal gold reaction was 444332100. Biopsy of the deltoid and vastus externus muscles showed marked atrophy and degeneration of the muscle fibers.

This patient entered the hospital with a fully developed syndrome of ascending paralysis. He had begun to recover before entrance and gave a history of ascending paralysis which had proceeded as far as the muscles of the neck. He recovered gradually, so that by the time of his discharge from the hospital he was much better, but by no means well. No etiologic factor could be discovered in his case except that on the day before the onset of his illness he had been to a picnic and had had transitory gastrointestinal disturbances.

CASE 7.—*Ascending weakness and later complete paralysis of all extremities, followed by facial diplegia and paralysis of respiratory muscles. Thirteen days in respirator, with subsequent complete recovery.*

History.—L. H., a woman aged 42, was admitted to the Philadelphia General Hospital on Feb. 5, 1938, in the service of Dr. J. C. Yaskin, complaining of inability to walk. She had been feeling poorly for several weeks. During the week before admission she had been to the receiving ward several times because of pain in the lower part of the back and weakness of the legs. The difficulty in walking was of five days' duration, and had become progressively more severe. There was no history of any antecedent infection or intoxication.

Examination.—On admission the patient was somewhat uncooperative, irritable and tearful. She could not stand, but did not seem otherwise disabled. There was no fever. She had incomplete facial diplegia, weakness of the arms and almost complete paralysis of the legs. The tendon reflexes of the arms were normal at this examination, and those of the lower extremities were absent. The abdominal reflexes and the Babinski sign were not obtained. There were no sensory disturbances aside from slight loss of vibratory sense in both lower extremities. Sphincter control was normal.

Course.—After admission to the hospital, the muscular weakness became rapidly more marked. Three days after admission intercostal breathing became suddenly impaired; the patient became dyspneic and was placed in a respirator. Her arms became very weak, and the biceps and triceps reflexes could not be obtained. Difficulty in swallowing developed. The patient remained in the respirator for thirteen days, when she seemed sufficiently improved to breathe independently. During the last few days in the respirator she had slight elevation in temperature, associated with a productive cough, proptosis of both eyeballs and marked swelling of the conjunctivas. These soon subsided as respiratory movements became normal.

From this point, her progress was one of steady recovery of muscle power, which returned first to the parts last affected. Shortly after the return of power, the tendon and abdominal reflexes returned. Neurologic examination three months after admission gave negative results except for slight facial weakness of peripheral type. Aside from mild clouding of the cornea, there was no disability on her discharge from the hospital.

Laboratory Findings.—Shortly after the patient was admitted to the hospital, response of the peripheral nerves to anoxia was measured. A series of measurements of the resistance of the ulnar and peroneal nerves to oxygen deprivation showed lowest values during the height of the paralyses and an increase to normal limits with recovery of function. These changes were identical with those observed

in cases of peripheral neuritis followed by recovery. The conventional reaction of degeneration was present only for two successive days.

Successive urinalyses showed occasional leukocytes. The serologic reactions of the blood were negative; sugar measured 107 and urea 13 mg. per hundred cubic centimeters of blood. Wassermann reaction of the spinal fluid was negative. The cell count of the spinal fluid was 1 cell per cubic millimeter.

The condition in this case was diagnosed as hysteria prior to the patient's admission to the hospital. This was due to the fact that the motor weakness was partial and that there was no systemic reaction, such as elevation in temperature or toxic phenomena. The prodromal period was of considerable duration; yet no etiologic cause could be found for the disease. Of great interest is the onset of paralysis of the intercostal muscles within two hours, indicating the need for careful watching in cases of this type, especially in view of the fact that this patient recovered largely with the aid of the respirator.

CASE 8.—*Chronic sinusitis, with acute exacerbation of a few days' duration, followed by ascending paralysis of all limbs within thirty-five hours and of abdominal, back and lower intercostal muscles in three days. No sensory or sphincter disturbances. Recovery.*

History.—E. W., a man aged 33, was admitted to the Graduate Hospital, in the service of Dr. R. A. Groff, on Jan. 4, 1939, with paralysis of all four extremities. He had had diphtheria at the age of 12, traumatic amputation of the right thigh at the age of 13 and repeated infection of the upper respiratory tract and sinusitis for a number of years. On Dec. 24, 1938, he had a recurrence of rhinitis and sinusitis, with considerable pain over the maxillary sinuses. A week later he first noticed weakness and stiffness of the left leg. Within the next twenty-four hours the weakness extended to both upper extremities, and on the following day he was completely paralyzed in all the limbs, could not sit up or turn the trunk and had such great weakness of the abdominal muscles that he had difficulty in defecation. On the next day he noticed difficulty in breathing. There was no history of pain, tingling or numbness, and no difficulty in micturition.

Examination.—Somatic examination gave normal results. The temperature, pulse rate and blood pressure were normal. There were no evidences of meningeal irritation. The cranial nerves were not involved. The muscles of the neck were normal. There was fairly good expansion of the upper part of the chest, with definite limitation of the lower part. The abdominal reflexes were absent. The abdominal muscles were paralyzed, and the patient was unable to turn from side to side. The anal sphincter had good tone. Power was good in the pectoral muscles and the external rotator muscles of the shoulder and slight in the deltoid muscles. There was complete paralysis of all the other muscles of the upper extremities on voluntary innervation. However, by use of the muscles of the shoulder girdle and gravity he managed to place his upper limbs in a variety of positions. The biceps and triceps reflexes were abolished. Examination of the lower extremities revealed movements of the stump of the right leg, but except for some power in the external rotator muscles of the left thigh, the left lower extremity was completely paralyzed. The knee and achilles reflexes were absent. There was no disturbance of sensation to pain, touch, heat, cold, position or vibration. There was no tenderness of the nerves except in the calf muscles, in which it was slight.

Course.—Throughout his residence in the hospital, the temperature and pulse remained normal. The patient was not toxic at any time and expressed no anxiety about his marked paralysis. During the few days following admission to the hospital his condition remained unchanged, except that from time to time shortness of breath developed. On the third day after admission there was definite improvement in thoracic expansion. On the fourth day some movements of the thumbs and fingers were noted. One week following this he had full expansion of the chest and some power in all the fingers and muscles of the wrist joints. Still a week later there were observed movements in the muscles of the elbow joint and return of the biceps and triceps reflexes. From then until his discharge from the hospital, on Jan. 28, 1939, there was continuous improvement, accompanied, however, by some atrophy, especially of the interossei muscles.

During the first five days of his residence in the hospital, he received sulfanilamide, 30 grains (1.95 Gm.) a day, and thereafter 3,000 units of thiamin chloride daily by intramuscular injection.

Laboratory Studies.—The spinal fluid pressure was normal; the fluid was clear and contained 18 cells per cubic millimeter, 52 per cent of which were lymphocytes and 48 per cent neutrophils; the total protein content was 23 mg. per hundred cubic centimeters and the Wassermann reaction and the colloidal gold curve were negative. The routine urinalysis and blood count were normal.

Second Examination.—The patient was seen at home on Feb. 5, 1939. He had shown considerable improvement in the use of most of his muscles. Power was good in the deltoid, and was markedly improved in the triceps, biceps, supinator longus and wrist muscles and in the flexor and extensor muscles of the fingers. The greatest weakness was still noted in the interossei and opponens pollicis; the right side showed much more improvement than the left. The biceps and triceps reflexes were present bilaterally. There was considerable improvement in the trunk muscles, and the patient was now able to rise and sit unassisted. The abdominal reflexes were still feeble. There was some return of power in the quadriceps and hamstring muscles and, to a lesser extent, in the adductors; the flexors and extensors of the feet and toes were still weak. The knee and achilles reflexes had not as yet returned.

Although the illness was initiated by an upper respiratory infection and the process was rapid, the patient was afebrile, showed no toxic symptoms and was singularly free from concern about his serious disability. A striking feature in this case was the agility with which he used the muscles of the shoulder and pelvic girdles to manipulate his flail-like, paralyzed limbs. Improvement commenced in the muscle groups which were last involved and progressed in the reverse order of the development of the paralysis.

CASE 9.—*Upper respiratory infection; weakness of the limbs, followed by almost complete paralysis, atrophy and loss of reflexes; no sensory disturbances. Frequent relapses. Gradual recovery.*

History.—N. R., a man aged 60, was referred by Dr. Paul Corman, of Bellefonte, Pa. He was well until January 1938, when he had a slight head cold followed by generalized weakness. After this he was again well until March 1938, when he had another cold followed by weakness in all four limbs. He was unable to work. He gave a vague history of ascending weakness of the limbs, beginning first in the feet, then involving the legs and finally the arms. He had no pain or fever at any time.

Examination.—The pupils were equal and regular and reacted promptly to light and in accommodation. The optic disks were well defined and of good color. There was a moderate degree of retinal arteriosclerosis. Ocular movements were full in all directions. The corneal reflexes were active. There was no weakness of the face, palate or tongue.

The upper extremities were very weak; the lower extremities had slight strength, but were still weak. The deltoid muscles were much weakened; the latissimus, pectoralis and teris major muscles were almost completely paralyzed. There was marked weakness of flexion and extension of the arms and of pronation and supination of the forearms. There was marked weakness of the hand grip on both sides. The hamstring, quadriceps and gastrocnemius muscles were weakened, but were less affected than the muscles of the arm. The quadriceps group was greatly atrophied; the hamstring and calf muscles were less involved.

All the muscles were soft and flabby. There were fibrillary twitchings in the triceps and in the first interosseous and thenar muscles.

The biceps, triceps, petellar and achilles reflexes were all absent. Babinski sign was not ilicited.

Pain, position, touch, heat and cold sensations were normal. There were no vesical or rectal disturbances.

Laboratory Studies.—Urinalysis gave entirely normal results. The red cell count was 4,960,000; the hemoglobin concentration was 100 per cent. The leukocyte count of the blood was 11,700, 74 per cent of which were polymorphonuclear cells. The spinal fluid pressure was 130 mm. of water. The fluid contained 2 cells per cubic millimeter; the protein content was not increased. The Wassermann reactions of the blood and spinal fluid were negative. There was no subarachnoid block. Roentgen studies showed few devitalized teeth. There was no evidence of carcinoma anywhere in the body. Electrical studies revealed no reaction of degeneration.

Course.—The patient was under direct observation for six months, but showed no real improvement. He made temporary gains, only to recede to his original state. With continued electrical treatment and physical therapy he has improved gradually, however, so that he is now able to walk and has regained much of his power.

This patient presented a picture of acute ascending paralysis. Like the condition in case 7, it was gradual in onset. In its full development it was a typical acute ascending paralysis. There were no evidence of neuritis at any time. Improvement was gradual as in other cases of this sort. No etiologic agent was suggested, except for the acute nasopharyngitis which preceded the onset.

HISTORICAL REVIEW

Interest in the role played by the spinal cord and peripheral nerves in paralyses of various sorts has been paramount in neurology since the time of Ollivier.[2] A steadily accumulating body of knowledge on this subject attracted the attention of Landry,[3] who collected a portion of the material into a monograph, published in 1859. In the same year

2. Ollivier, C. P.: Traité de la moelle épinière et de ses maladies, Paris, Crevot, 1827.

3. Landry, J. B. O.: Traité complet des paralysies, Paris, V. Masson, 1859.

he published an observation of a case of acute ascending paralysis, a brief abstract of which follows:

A laborer, aged 43, was ailing for one year before his death. For a few weeks before the onset of paralytic symptoms he complained of acroparesthesias of his fingers and toes and generalized weakness. He walked a great distance to the hospital, where he arrived on June 1, 1859. On June 13, 1859 his legs became very weak, and the tingling sensations spread to his legs and arms. In a few days more or less complete paralysis was present in all extremities, and, shortly thereafter, the muscles of the trunk and diaphragm became weak. There was no pain or mental impairment. His temperature remained normal, and control of the bowels and bladder was unimpaired. There was some blunting of sensibility in the peripheral parts of the limbs. The paralyzed muscles could be excited by faradic current, and there were no contractures. As respiration became more labored, there appeared weakness of the muscles of mastication and of the tongue; the extraocular muscles were not affected. A sense of constriction about the thorax and numbness in the limbs were complained of. The patient died suddenly on June 25, 1859. No gross changes were observed post mortem, except for pleural adhesions. Careful microscopic examination of the spinal cord did not reveal pathologic changes. The peripheral nerves were not examined.

In this and in a subsequent paper in which he reported 10 cases, Landry established the following diagnostic criteria for this disease: (1) symptoms of rapidly ascending motor paralysis, without atrophy, contracture or electrical changes; (2) absence of or slight sensory phenomena; (3) freedom from sphincter disturbances; (4) absence of pathologic changes.

It is largely due to Vulpian [4] that this syndrome has become known as "Landry's disease," as he first referred to it as such. Since then, the terms "Landry's paralysis" and "acute ascending paralysis," which was Landry's own term, have been used interchangeably.

DEFINITION

Since the Landry syndrome has so many varieties and occurs in so many conditions, it seems advisable to review the criteria for the diagnosis of this syndrome in order to establish as great a degree of uniformity as possible. The criteria laid down by Landry in 1859 seem to need revision in view of later knowledge. Since Landry's original description, much has been learned about the syndrome which bears his name.

A survey of the cases reported, as well as of our own, indicates that under the syndrome of acute ascending paralysis should be included conditions with the following features: an onset of bilateral symmetric paralysis in the legs; rapid or gradual extension to involve muscles of the

4. Vulpian, E. F. A.: Les maladies du système nerveux, leçons professées à la faculté de médecine de Paris, Paris, O. Doin, 1879, vol. 6, p. 189.

arms and trunk, sometimes the muscles of swallowing, occasionally those of mastication and phonation and rarely ocular movements; loss or diminution of tendon reflexes, and usually, but not always, presence of sphincter disturbances and absence of any marked sensory disturbances.

GENERAL CLINICAL FEATURES

The clinical features of acute ascending paralysis are variable and often atypical—hence the numerous problems which arise in the diagnosis of this seemingly easily recognized entity. The typical form is readily diagnosed. It begins abruptly in a person who has had a nasopharyngeal infection shortly before the onset, or there may be no prodromal symptoms whatever. The onset is often with fever, but the disease may be entirely afebrile in its onset, and even in its entire course. Systemic symptoms are usually present and consist of malaise, vomiting, a feeling of profound fatigue or aching of the muscles. Within a short time there is weakness of the legs, leading quickly to complete paralysis. Then follows gradually or rapidly ascending paralysis, involving the abdominal and thoracic muscles and finally the arms. The vesical and rectal sphincters may or may not be involved. The illness may progress no farther than the arms. It usually advances to effect the muscles of deglutition and respiration, as a result of involvement of the centers in the medulla. Ocular paralyses, paralysis of the muscles of chewing and aphonia may develop. In most cases the course (80 per cent) terminates in death, but in some instances there is partial or complete recovery.

Examination reveals flaccid, atonic muscles which are usually completely paralyzed. The tendon reflexes are absent as a rule. Sensory disturbances are not usually present. Laboratory studies are not of much help in the diagnosis. There is usually no leukocytosis, and the findings in the spinal fluid are generally normal.

The diagnosis of acute ascending paralysis is easy in a case in which there are fever, a history of ascending paralysis and signs of flaccid paralysis of the limbs. When one is confronted with a case in which there is no fever the diagnosis may be difficult to accept. It should be recognized, however, that in most cases of acute ascending paralysis fever and systemic reactions are not present. For this reason, the diagnosis of hysteria is not uncommonly made in such cases, and great care should be exercised to avoid this error.

The syndrome of acute ascending paralysis has been found in many conditions. It has been described in cases of Landry's syndrome, of poliomyelitis, of disseminated encephalomyelitis, of syphilis of the spinal cord and of peripheral neuritis. Its occurrence in such a wide variety of conditions makes necessary the determination in each case of the presence of any of these or of other conditions.

SPECIAL FEATURES

The variability in some of the specific features of acute ascending paralysis often leads to confusion in diagnosis. Hence, analysis of some of these features is indicated.

Onset.—The onset varies in different cases of acute ascending paralysis. Of 79 cases in which information is available in the literature the onset was acute in 43, or 54 per cent, with prodromal symptoms lasting forty-eight hours or less; in 15 cases, or 19 per cent, the prodromal period was from two to five days; in 7, or 9 per cent, from six to ten days, and in 14, or 18 per cent, more than ten days. In most cases, therefore, the time between the first appearance of prodromal symptoms and the first appearance of weakness was short, and in only a few cases was it more than five days.

The length of time required for development of the picture of complete paralysis was noted in 87 cases. This period varied from immediate development to twelve hours in 9 per cent of the cases, from twelve to forty-eight hours in 11 per cent, from two to four days in 31 per cent, from four to ten days in 33 per cent and longer than ten days in 15 per cent.

Fever.—Fever of some degree is often present; it is by no means invariable, however, and there should be no hesitation in making the diagnosis when fever is absent. Of 103 cases described in the literature in which the temperature was recorded, normal levels were maintained throughout the course of the disease in 70, or 67 per cent. In only 26, or 25 per cent, of the cases was there elevation of temperature; in 7, or 6.7 per cent, there was a terminal increase. It is probable that in the cases in which a terminal rise in temperature developed, and in some other cases as well, fever resulted from an intercurrent complication. Fever as a rule is not high in acute ascending paralysis. A temperature of 100 or 101 F. is common, but higher temperatures may occur.

Ascension of Paralysis.—Some textbooks of neurology, in discussing acute ascending paralysis, make the point that the process may at times have a descending progression. Of 111 cases in the literature in which information on this point is available, the progression of paralysis was definitely downward. Of the remaining 110 cases, the paralysis was ascending in 93 per cent, and the paralytic symptoms appeared simultaneously in the arms and in the legs in 7 per cent.

Distribution of Paralyses.—The paralytic symptoms are most often noted first in the large muscles of the thigh or the upper portion of the arm. This is not conclusive evidence that these muscles are affected first, as the larger muscles labor under greater mechanical disadvantage than the small muscles of the hands and feet. Thus some degree of

weakness would be noted first in the larger muscles. Another point of interest concerning the distribution of paralyses in cases of the fully developed clinical syndrome is the relative frequency with which the arms, legs and face are involved. Of 116 cases reported in the literature, the legs were affected in 116, or 100 per cent; the arms in 109, or 93 per cent, and the face in 23, or 20 per cent. The presence or absence of muscular atrophy was mentioned in only 14 of 125 cases; it was present in 9 and absent in 5. These figures do not represent the correct statistical frequency with which muscular atrophy occurs, as there is probably a tendency not to mention it when it is absent. Similarly, fibrillation was mentioned in 6 cases, being present in 4 and absent in 2.

Sensory Disturbances.—These were noted in 39 of 103 cases recorded in the literature. They varied greatly in type, from lesions of level distribution to scattered disturbances of various kinds. Tenderness of the calf muscles was noted in 25 per cent of the cases.

Sphincter Disturbances.—These were found in 48 of 96 cases, or in 50 per cent. There was a distinct tendency for the sphincter disturbances to occur in cases in which sensory disturbances were present or in cases in which there was fairly extensive damage to the cord.

Disturbances in Reflexes.—The tendon reflexes were absent or decreased in all cases.

Laboratory Findings.—There are no significant, constant laboratory findings which occur in any great percentage of cases of acute symmetric ascending paralysis. This is understandable from consideration of the variety of etiologic and pathologic conditions with which the syndrome is associated. The leukocyte count of the blood ranged in 61 cases from 5,200 to 37,500 per cubic millimeters, the average count was 8,250, and the mode, 9,700. The erythrocyte count of the blood varied in 43 cases from 2,890,000 to 5,950,000, with an average of 4,690,000 and a mode of 4,950,000. The cell count of the cerebrospinal fluid ranged from 0 to 2,100, with an average of 40 and a mode of 0. In 21 cases the colloidal gold curve was of a midzone, or dementia paralytica, type. There were no significant alterations in the level of protein, sugar or chlorides in the spinal fluid.

ETIOLOGIC FACTORS

In at least 30 per cent of cases of acute ascending paralysis there is no clue as to the cause, either in the pathologic study of the nervous system and other organs of the body or in the clinical features. In many of these cases the paralysis appears to follow closely on the heels of an infection, particularly of the respiratory tract. At best, the etiologic factor in this group is still sufficiently obscure to be a matter of

conjecture. In a small number of cases in which no pathologic lesions may be demonstrated the cause is accurately known. The best example of this type is "tick" paralysis. This form of acute ascending paralysis is caused by the bite of a tick and occurs in sheep,[5] dog [6] and man.[7] The paralysis is symmetric, ascending and flaccid. It is accompanied by loss of reflexes, but not by fever. On removal of the tick, which is generally lodged at the hair line at the back of the neck, the symptoms promptly subside in the reverse order of their appearance, leaving no sequelae. Experimental work has not demonstrated whether the saliva of the tick or some infective agent in the saliva is responsible for the paralytic phenomena. The disease is largely limited to the Rocky Mountain region and to Australia.

Acute ascending paralysis may also be caused by the sting of a weaver fish (Trachinus draco),[8] vaccine therapy [9] or antitetanus inoculation,[10] or it may be associated with hematoporphyrinuria [11] and with pregnancy.[12]

Acute ascending paralysis may occur in association with pathologic processes elsewhere in the body. Among these are typhoid fever,[13]

5. Hadwen, S.: On Tick Paralysis in Sheep and Man, Parasitology **6**:283, 1913.

6. Hadwen, S., and Nuttall, G.: Experimental "Tick Paralysis" in the Dog, Parasitology **6**:298, 1913.

7. Nuttall, G.: "Tick Paralysis" in Man and Animals, Parasitology **7**:95, 1914. Bassoe, P.: Paralysis of Ascending Type in an Adult Due to Bite by a Woodtick, Arch. Neurol. & Psychiat. **11**:564 (May) 1924.

8. Schulmann, E., and Ravier, J. L.: Paralysie ascendante mortelle due vraisemblablement à une piqûre de vive (Trachinus draco), Progrès méd. **44**:2190, 1929.

9. Leahy, W. R.: Death Following Closely upon Administration of Cold Vaccine, U. S. Vet. Bur. M. Bull. **6**:506, 1930. Olmer, J., and Paillas, J.: Accidents de type sérique et syndrome de Landry apres vaccinotherapie, Paris méd. **2**:236, 1935. Guillain, G., and Barré, J.: Paralysie ascendante aiguë de Landry consécutive à une vaccination antityphoïdique, Ann. de méd. **6**:218, 1919.

10. Lerond, J.: Syndrome de paralysie ascendante, Bull. et mém. Soc. méd. d. hôp de Paris **50**:1695, 1926.

11. Blum, H. F., and Schumacher, I. C.: Abnormal Sensitivity to Light in a Case of Possible Landry's Paralysis, Ann. Int. Med. **11**:548, 1937. Magendantz, H.: Ein Fall von akuter Porphyrie, Nervenarzt **9**:76, 1936. Courcoux, A.; Lhermitte, J., and Boulanger-Pilet, G.: La paralysie extenso-progressive hématoporphyrique: Etude anatoma-clinique, Presse méd. **37**:1609, 1929.

12. Caffier, P., in discussion on Creutzfeldt, H. G.: Zur Pathogenese—Pathologie von Landryscher Lähmung, Ztschr. f. Geburtsh. u. Gynäk. **97**:553, 1930. Hornung, R.: Bilder von Lähmungen (Typus Landry) in der Schwangerschaft, ibid. **97**:546, 1930. Hornung, R., and Creutzfeldt, H. G.: Lähmungen vom Landryschen Typ in der Schwangerschaft, Deutsche med. Wchnschr. **56**:1470, 1930.

13. Leon-Kindberg, M., and Garcin, R.: Paralysie ascendante aiguë mortelle vraisemblablement névritique au cours d'une fièvre typhoïde, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1340, 1928.

herpes zoster,[14] lymphogranuloma with the absence of lymphogranulomatous infiltration of the nervous system,[15] malaria,[16] leukemia with leukemic infiltration of the spinal cord[17] and systemic infections of various kinds. One of the most important causes of acute ascending paralysis is rabies and antirabic vaccine.[18] In a small number of cases of epidemic anterior poliomyelitis there may be clinical symptoms resembling the symmetric ascending paralysis syndrome.

PATHOLOGIC FEATURES

The pathologic basis for these clinical phenomena is perhaps the most interesting feature of this syndrome. Of 78 cases in the literature which were studied pathologically, absence of lesions was reported in 24, or 30 per cent. Two sources of error, which tend to neutralize each other to a certain extent, are innate in these statistics. Some cases reported were not completely studied, and in other cases minor pathologic appearances, such as may be within the range of normal variations, were mentioned as significant. On the whole, the latter factor is probably more important numerically; this would place as too low the estimate of 30 per cent of cases in which no lesions were shown.

Of the 30 cases reported in which "degenerative" lesions were present, the peripheral nerves alone were involved in 14, or 46 per cent; the spinal cord, in 11, or 36 per cent and the cord and the peripheral nerves in 5, or 15 per cent. The degenerative changes in the cord involved chiefly, and at times solely, the anterior horn cells. In many of the cases in which only the anterior horns were involved the changes were slight, and, in view of the rapid changes which take place soon after

14. Remlinger, P., and Bailly, J.: Contribution à l'étude du virus herpétique (souche marocaine), Ann. Inst. Pasteur **41**:1314, 1927. Schuback, A.: Herpes zoster und Landrysche Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:424, 1930.

15. Környey, S.: Aufsteigende Lähmung und Korsakowsche Psychose bei Lymphogranulomatose, Deutsche Ztschr. f. Nervenh. **125**:129, 1932.

16. Smirnow, L. I.: Die pathologische Anatomie und Pathogenese der Paralysis ascendens acuta, Arch. f. Psychiat. **78**:585, 1926. Skobsky, J. L.: Akute aufsteigende Paralyse mit regressivem Verlauf, Monatschr. f. Psychiat. u. Neurol. **90**:169, 1934.

17. Cornil, L.; Olmer, D.; Olmer, J., and Alliez: Paralysie ascendante de Landry, Sang **6**:114, 1932.

18. Stuart, G., and Krikorian, K. S.: A Fatal Neuroparalytic Accident of Antirabies Treatment, Lancet **1**:1123, 1930. Knutti, R. E.: Acute Ascending Paralysis and Myelitis Due to the Virus of Rabies, J. A. M. A. **93**:754 (Sept. 7) 1929. Palthe, P. M.: Acute Ascending Paralysis as a Manifestation of Rabies, Nederl. tijdschr. v. geneesk. **74**:2108, 1930. Lemke, R.: Ueber ein Fall von abortiver Lyssa unter dem Kranksheitsbild der Landryschen Paralyse, Arch. f. Psychiat. **102**:140, 1934.

death, it is possible that these cases, too, may be classified more properly under the heading of "no lesion." In many cases pathologic examination was confined to the cord alone, but in no case to the peripheral nerves alone. In the first group, descriptions suggesting axonal chromatolysis indicate that lesions of the peripheral nerves (which were not examined in this group) may have been more frequent than the figures show. Twenty-four cases are described in which inflammatory lesions were predominant. Of these, the lesions involved the spinal cord only in 15, or 62 per cent; the peripheral nerves only in 6, or 25 per cent; and both the peripheral nerves and the spinal cord in 3, or 12 per cent. These lesions varied from the most intense to the slightest inflammatory changes. An attempt has been made by Kaldewey [18a] to establish "polioclastic myelitis" as a pathologic entity in which the severity of the lesions is just short of that in poliomyelitis. Many of the changes noted would not be universally acceptable criteria of an inflammatory process. For this reason, the figure given for the incidence of inflammatory lesions is probably too high.

In general, it has not been possible to predict the pathologic changes noted post mortem from the clinical observations made during life. In all of the 24 cases reported in which there were no pathologic lesions in the nervous system the temperature was normal, and sphincter disturbances were present in only 1, a case in which psychotic symptoms were also manifested. In no case in this group was there any considerable degree of objective sensory disturbance. The onset may or may not have been preceded by a period of illness. In a general way it may be stated that the greater the amount of disturbance in sensation, sphincter control or temperature the more likely are pathologic lesions to be demonstrable.

The pathologic background in cases of acute ascending paralysis has always been elusive. It has been a constant surprise to find cases in which there were profound objective neurologic changes and few or no evidences of damage in the nervous system. The great variability in the findings suggests, first, that included under the acute ascending paralysis of Landry are many types of the disease for which there are different causes, and, second, that, as for example in botulism, the primary damage may not necessarily be within the nervous system. This is a concept which is difficult to accept in respect to a disease which seems to be so exquisitely neurogenic in origin.

It is impossible to define a specific pathologic picture of acute ascending paralysis. This has long been recognized. Diagnosis, either grossly

18a. Kaldewey, W.: Landrysche Paralyse, Porphyrie, Sulphonal, Ztschr. f. d. ges. Neurol. u. Psychiat. **145**:165, 1933.

or microscopically, is impossible. One sees a variety of pictures, in which the changes in the nervous system vary from those within the normal range or minimal pathologic alterations to severe degenerative and inflammatory lesions. The findings suggest strongly, therefore, that no one causative agent produces the similar clinical pictures known as acute ascending paralysis of Landry.

The specific changes are as confusing as they are variable. In the case of Dejerine,[19] lesions were observed in the anterior roots consisting of degeneration of myelin, multiplication of the Schwann nuclei and degeneration of the axis-cylinders. No changes were seen in the spinal cord. Similarly, in the case described by Juba and his associates [20] no changes were seen in the spinal cord, but fatty degeneration was present in both sciatic nerves and degeneration of the spinal ganglion cells with lymphocytic infiltration of the ganglia was also observed. In 1 of the cases of Roosen-Runge [21] the spinal cord showed no changes; in another, typical changes of poliomyelitis were seen.

In a case of severe paralysis of the arms and legs Drake [22] observed only mild degenerative changes in the anterior horn cells and the cells of the column of Clarke. The anterior and posterior roots were normal. Chromatolytic changes were seen in the nuclei of the hypoglossal and vagus nerves. On the other hand, in a case recorded by Milark [23] in which the clinical manifestations were almost as severe, only mild shrinkage of the anterior horn cells, hyperemia and perivascular infiltration, hardly enough to explain the severe clinical manifestation, were present.

At times the changes seem to be chiefly in the spinal roots and nerves, as in the case reported by Gärtner.[24] In this case the paralysis was severe, with bulbar symptoms. The spinal cord was normal except for slight infiltration of some of the cervical and thoracic segments. The anterior and posterior roots, especially in the lumbar region, showed degeneration and lymphocytic infiltration. Similar alterations were seen

19. Dejerine, J.: Recherches sur les lésions du système nerveux dans la paralysie ascendante aiguë, Thesis, Paris, no. 72, 1879.

20. Juba, A., and Szatmari, A.: Landryartige Polyradiculoganglionitis bei einem Syphilitiker, Deutsche Ztschr. f. Nervenh. **142**:28, 1937. Juba, A.: Ueber einem perakut verlaufenden Fall von Polyneuroganglioradiculitis ascendens, ibid. **142**: 265, 1937.

21. Roosen-Runge, E.: Zum Syndrome der Landryschen Paralyse, Nervenarzt **10**:301, 1937.

22. Drake, R.: Acute Ascending Paralysis, M. Rec. **142**:232, 1935.

23. Milark: Ein Fall von Poliomyelitis ascendens acutissima (Landryschen Paralyse), Deutsche med. Wchnschr. **59**:890, 1933.

24. Gärtner, W.: Poly-Neuro-Radiculitis ascendens, Deutsche Ztschr. f. Nervenh. **123**:18, 1931.

in the vagus and the sciatic nerves. Demme [25] recorded a similar case. In this case the spinal cord showed no changes except for lymphocytic infiltration in the root entrance zone and in the meninges. In the peripheral nerves, on the other hand, degeneration of the axis-cylinders and lymphocytic infiltration were evident. In the spinal ganglia there was lymphocytic infiltration, but no degeneration of the ganglion cells. In Thomas' [26] case degenerative alterations were observed in the peripheral nerves, combined with changes in the anterior horn cells. Diffuse degeneration in the peripheral nerves, with evidences of interstitial neuritis unaccompanied by changes in the cord, were recorded in 2 cases by Hollander and Karoliny.[27] More purely degenerative changes in the peripheral nerves and anterior spinal nerve roots were reported in 3 cases by Adler and Hoff.[28] A particularly interesting example of the "neuritic" type of acute ascending paralysis is seen in the case recorded by Büttner, in which demyelination and changes in the axis-cylinders occurred in the roots of the cauda equina. Pette and Környey [29] recorded 2 cases in which changes were chiefly in the spinal nerve roots and spinal ganglia.

Probably because of these observations, acute ascending paralysis has come to be regarded by some investigators as primarily a peripheral neuritis. Indeed, not a few cases are recorded in the literature under such titles as polyneuritis or polyradiculoneuritis. In so far as the pathologic observations are concerned, there is no conclusive evidence that acute ascending paralysis is a primary neuritis. In some cases, to be sure, there are destructive changes in the peripheral nerves, but these are seldom present without evidences of damage elsewhere in the nervous system. They are rarely seen alone. The few instances in which the nerves or the nerve roots alone are affected do not form a basis for the assumption that the acute ascending paralysis of Landry is in all instances a multiple neuritis.

Severe changes in the spinal cord have been described in some cases, but there was no uniformity in the type or distribution of the damage

25. Demme, H.: Zur Pathogenese der entzündlichen Form der Landryschen Paralyse, Deutsche Ztschr. f. Nervenh. **125**:1, 1932.

26. Thomas, J.: Two Cases of Acute Ascending Paralysis, Am. J. M. Sc. **116**:133, 1898.

27. Hollander, L., and Karoliny, L.: Beiträge zur Pathologie und Aetiologie der Landryschen Paralyse, München. med. Wchnschr. **75**:1549, 1928.

28. Adler, A., and Hoff, H.: Gehäuftes Auftreten von Polyneuritiden unter dem Bild zur Landryschen Paralyse, Deutsche med. Wchnschr. **55**:1880, 1929.

29. Pette, H., and Környey, S.: Zur Histologie und Pathogenese der akut-entzündlichen Formen der Landryschen Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:390, 1930.

to the nervous system. Brussilowsky,[30] for example, described severe parenchymatous changes in the spinal cord, involving by an acute process many of the cells of the anterior horns and the column of Clarke. The process was apparently so acute that glial changes were few. There were also diffuse degeneration of the myelin in the spinal cord and destruction of both myelin and axis-cylinders in the peripheral nerves. Endarteritic changes were present in the vessels. Sometimes the changes in the nervous system have been characterized largely by marked evidences of inflammation, as in the case reported by Read, Conley and Conley.[31] Here, the changes in the ganglion cells were overshadowed by the heavy perivascular infiltrations of lymphocytes and plasma cells in the gray matter of the spinal cord and the medulla. Similar infiltrations were observed in the interstitial tissue and in the nerve roots. Similar cases were recorded by Pawljutschenko [32] and by Marie and Tretiakoff.[33] The latter authors described many necrotic and inflammatory lesions involving the anterior horns throughout the length of the cord in 1 case, discrete inflammatory lesions in the anterior horns and brain stem in another case and what they called diffuse leukoencephalomyelitis, characterized by acute degenerative vascular lesions in the white substances of the brain, in a third case. The diagnosis in the third case appears to be questionable. In some instances degenerative changes involving the anterior horn cells predominate over the inflammatory lesions, which are seen in mild perivascular cuffings. This is true of the cases recorded by Callewaert [34]; by Shafar [35]; by Goldby [36]; by Getzowa, Stuart and Krikorian,[37] and by Dimitri.[38] In the cases reported by Dimitri the anterior horn cells were severely damaged in the spinal cord and sometimes in the brain stem; punctate hemorrhages were seen in the affected areas.

30. Brussilowsky, L.: Zur Lehre von der akuten aufsteigenden Landryschen Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:515, 1927.

31. Read, C. F.; Conley, T. E., and Conley, H. H.: Acute Ascending Paralysis: Landry Syndrome; Prolonged Use of Artificial Respirations; Death and Autopsy, J. A. M. A. **94**:557 (Feb. 22) 1930.

32. Pawljutschenko, E. M.: Zur Klinik und pathologischen Anatomie der akuten aufsteigenden Landryschen Paralyse, Arch. f. Psychiat. **89**:570, 1930.

33. Marie, P., and Tretiakoff, C.: Etude anatomo-pothologique de trois cas de maladie de Landry à forme médullaire, Rev. neurol. **37**:777, 1921.

34. Callewaert, P.: Deux observations anatomo-cliniques de Landry, J. belge de neurol. et de psychiat. **36**:368, 1936.

35. Shafar, J.: Acute Ascending Flaccid Paralysis, Lancet **1**:1275, 1937.

36. Goldby, F.: Landry's Paralysis, J. Neurol. & Psychopath. **11**:1, 1930.

37. Getzowa, S.; Stuart, G., and Krikorian, K. S.: Pathological Change Observed in Paralysis of the Landry Type, J. Path. & Bact. **37**:483, 1933.

38. Dimitri, V.: Paralysis ascendente aguda, Rev. de especialid. **5**:72, 1930.

In not all the cases in which there are definite pathologic changes is damage as severe as in those which have been cited. Evidences of mild chromatolysis of the anterior horn cells of the spinal cord and of some of the ganglion cells in the cortex were found by Courville and Mason [39] and by Ley and van Bogaert.[40] Similar changes were present in the cases of Babonneix and Duruy,[41] Pines and Maiman,[42] Mills and Spiller [43] and Vires and Serre.[44]

It is obvious, therefore, from a review of the recorded cases, that there is no uniformity whatever either in the type or in the distribution of the lesions described. In many cases the picture is entirely normal. In others inflammatory lesions, much like those in poliomyelitis, predominate; in others degenerative changes with evidences of secondary or symptomatic inflammation, and in still others alterations in the peripheral nerves and nerve roots, are most frequent. As a rule, in cases of the severe form lesions are widespread and involve the spinal cord and brain stem, whereas in cases of the milder type they are only scattered. It seems inconceivable, from a review of the pathologic changes, that acute ascending paralysis can be due to a single etiologic agent in all cases. The lesions are too variable and show no specific factor common to every case. Regardless of the severity of the lesions in poliomyelitis or in dementia paralytica, for example, there is a type of pathologic change common to all cases. This cannot be said to be true in cases of acute ascending paralysis. Neither can the various types of lesions described be regarded as different stages of a single process. There appears to be only one logical conclusion, namely, that acute ascending paralysis is caused by a variety of agents and that no one cause accounts for all the lesions described.

This much can be said: In most of the cases recorded in which definite pathologic lesions were present, the anterior horn cells or their processes (nerves or nerve roots) were diseased. The problem is to

39. Courville, C. B., and Mason, V. R.: Acute Ascending Paralysis (Landry's Paralysis) with Acute Idiopathic Hematoporphyria, Arch. Neurol. & Psychiat. **25**:848 (April) 1931.

40. Ley, R. A., and van Bogaert, L.: Paralysie ascendante de Landry avec névrite optique double sans lésions histologiques décelables, J. belge de neurol. et de psychiat. **34**:490, 1934.

41. Babonneix, L., and Duruy, A.: Paralysie ascendante aiguë, Rev. neurol. **1**:643, 1929.

42. Pines, J., and Maiman, R.: Beitrag zur Lehre von der Paralysie Landry, Arch. f. Psychiat. **79**:175, 1926.

43. Mills, L. K., and Spiller, W. G.: On Landry's Paralysis, J. Nerv. & Ment. Dis. **25**:365, 1898.

44. Vires, and Serre, H.: Syndrome de Landry clinqiuement primitif, Arch. Soc. d. sc. méd. et biol. de Montpellier **17**:286, 1936.

determine the basis of the disease in cases in which no lesion is discovered. It is possible that in such cases the difficulty lies in the myoneural junction. That widespread involvement of this structure may occur has been shown in cases of curare poisoning and of botulism. It is conceivable that physiologic disruption may occur at the myoneural junctions in some cases of acute ascending paralysis.

CONCLUSIONS

In this paper we have discussed acute symmetric ascending paralysis and have presented illustrative cases.

The etiologic agent is unidentified in at least 30 per cent of the cases, and varies in the remainder.

The syndrome is dependent on a pathophysiologic lesion of the lower motor neuron, but the exact location is not always clear. In some cases the anterior horn cells are involved, but in many there is no evidence of their damage. It is possible that in such cases the disturbance may be at the myoneural junction.

The term "Landry's paralysis" should be discarded for the following reasons: (*a*) It is not descriptive; (*b*) it assumes that there is no demonstrable lesion of the nervous system, an assumption which cannot safely be made on the basis of the clinical picture alone; (*c*) the term "acute ascending paralysis" is more descriptive.

DISCUSSION

Dr. George Gammon, Philadelphia: In this series of cases, is there any significance in the time element? In the different types of cases which have been described, and in those in which the patients recovered, what of the time element and the etiologic factors? Does the disease require a longer time to develop in some cases and less in others?

Dr. Eli Marcovitz, Philadelphia: What of the use of vitamin B_1 in cases of Landry's paralysis?

Dr. Milton K. Meyers, Philadelphia: It is likely that in the past cases were not studied in a way which would compare satisfactorily with modern neuropathologic methods. What was the etiologic agent in the 9 cases the authors observed personally?

Dr. Michael Scott, Philadelphia: What was the type of infection in the cases reported in the literature and in some of the authors' own cases? In cases in which there were inflammatory lesions was there any lymphocytic response?

Dr. J. C. Yaskin, Philadelphia: There are some points that Dr. Thorner could not mention, owing to lack of time. I wish to stress especially the confusion of Landry's paralysis with hysteria. That may sound remote, but the error is not rare.

In case 7, in which also malingering was suspected because of absence of fever, the patient recovered. The appearance of such patients is deceptive.

Dr. Charles Smith, Philadelphia: I wish to ask Dr. Thorner whether he noted any instances of anuria in the 9 cases presented. Last year a patient walked into the hospital with numbness and tingling of the feet. Three or four hours later

he had anuria, paralysis progressing to the upper extremities and respiratory paralysis. Although there was no autopsy, I think this case might be listed as one of Landry's ascending paralysis.

Dr. Temple Fay, Philadelphia: What intrigues me is the uniformity with which the symptoms ascend, in view of the fact that it is not a cervical process or an inflammation affecting the long fibers alone. It seems unique that any condition could begin in the lower part of the cord and gradually "climb the ladder," segment by segment; it almost predicates an anatomic and structural basis.

In view of the cases which I have reported in which meningorachidian phlebitis gave rise to ascending paralysis, I wish to ask whether cultures revealed Streptococcus viridans in any of the present cases.

Dr. Batson showed me injections of the venous system about the cord, extending from the dorsal vein of the penis to the occipital veins at the base of the brain. There is the possibility, therefore, of venous flow from the dorsal and distal portion of the cord to the occipital and basilar region of the brain. He has shown that obstruction of the abdominal veins or straining may permit blood to "by-pass" the abdominal route, using the spinal system instead. I have seen, in neurosurgical practice, several cases of unexplained epidural abscesses involving the fifth thoracic level, in 2 of which the origin was gonorrheal. I think that a vascular continuity may exist between pelvic, rectal and urethral infections and the external venous system about the spinal cord, as suggested by the anatomic observations of Dr. Batson.

Dr. Bernard J. Alpers, Philadelphia: There are two points I wish to make regarding terminology. First, this group of acute ascending paralyses represents a pure and a large heterogeneous subgroup—pure Landry's paralysis with no changes in the nervous system and paralyses which may occur with varied pathologic conditions, such as poliomyelitis and rabies. This should be kept in mind with regard to Landry's paralysis.

Second, I agree heartily with Dr. Yaskin regarding the differential diagnosis of hysteria. I have had that to make in 2 cases. One (case 1) was that of a male nurse who had been on a picnic and had eaten canned food. In the hospital ward he was regarded as having hysteria and was forced to get out of bed. Two hours after I made an examination the patient was placed in a respirator; he died as a result of medullary involvement. Unquestionably, the differential diagnosis is made largely because the patients are afebrile.

There is a tendency in these days to regard Landry's paralysis as peripheral neuritis. I do not know what the evidence is for that point of view. For example, in cases in which pathologic observations have been reported, the peripheral nerves were frequently normal. Many such instances exist, and I, personally, fail to see that a case has been made for Landry's paralysis as peripheral neuritis.

Dr. Melvin W. Thorner, Philadelphia: The question of the time relation between the stage of development and that of recovery cannot adequately be answered from the data available. Less than 150 cases of acute ascending paralysis have been reported, and in only 20 per cent of these did the patient recover. This is too small a number of cases from which to answer the question. The possibility of a relation of vitamin B_1 deficiency to this syndrome is a matter of conjecture. The period required for recovery in favorable cases of acute ascending paralysis is usually much shorter than those seen in cases of the deficiency neuropathies. Still employment of the vitamin in these cases could do no harm.

The etiologic factor in the cases reported here cannot be stated with certainty. In each instance there were possible explanations, but evidence to indict any one

factor was insufficient. In a significant number of cases a mild infection of the upper respiratory tract antedated the paralysis.

For Dr. Fay's comment on the possible mechanism of this unique syndrome I have no answer, although it is not for lack of thinking on this problem. The bilateral symmetry of the paralysis, the orderly ascension, and, in favorable cases, the recession of the symptoms in the reverse order of their appearance, the relative sparing of the sensory apparatus in such a widespread process—all these features are difficult to explain. It is evident that in some instances (as in case 7) the pathologic process involving the lower motor neuron is reversible. Even here, however, one would expect recovery to occur in the same order as that in which the paralysis occurred. Because the apparent etiology is so varied, the possibility of distinguishing a single mechanism common to all cases seems remote.

DURAL HEADACHE AND INNERVATION OF THE DURA MATER

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The only adjective which Celsus applied to headache was "intolerabilis." Unless it was intolerable, he said, there was no necessity for a remedy (Vaughan, 1825 [1]). Today the same proviso might be applied, at least to surgical remedies. But when the ache is intolerable, radical operative treatment should be undertaken. Knowledge of the innervation and sensitivity of intracranial structures is prerequisite to success with such treatment. This study is concerned primarily with the nerve supply and pain reference of the dura mater in man and in the monkey. It is illustrated by clinical cases which cast light on dural sensitivity and on the radical treatment of falcial cicatrix, migraine and other forms of headache. A preliminary anatomic study has already been published by one of us (F. M.).[2]

STRUCTURE AND DEVELOPMENT OF THE CEREBRAL DURA MATER

The cerebral dura is a very tough membrane composed of two closely adherent layers containing much collagen and elastic tissue. The connective tissue bundles of the two layers tend to be placed at right angles to one another so that the dura, which lines the inner surface of the skull and forms the dural reflections, including the falx and the tentorium cerebelli, is rigid and resistant to stretching.

The large venous sinuses lie between the two dural layers, while the meningeal arteries lie mainly in the outer, or endosteal, layer. The principal blood supply comes through the middle meningeal artery, although there are a number of less important arteries, including the anterior meningeal artery (from the ethmoid arteries), in the anterior fossa on each side, the accessory meningeal artery, in the middle fossa, and also fine branches leaving the internal carotid artery to supply the dura of the middle fossa and the tentorium, and the posterior meningeal arteries (branches of the vertebral, ascending pharyngeal and occipital arteries), within the posterior fossa.

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Read in part at the Sixty-Fourth Annual Meeting of the American Neurological Association, Atlantic City, N. J., May 3, 1938.

1. Vaughan, W.: Essay on Headaches, London, 1825.

2. McNaughton, F.: The Innervation of the Intracranial Blood Vessels and Dural Sinuses, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:178-200, 1938.

The arachnoid is separated from the inner surface of the dura by a thin layer of fluid, which is normally to be found in the subdural space. This space is crossed by the large pial veins entering the venous sinuses, by the cranial nerves and great arterial trunks at the base and by the arachnoid granulations which attach the hemispheres to the dura at certain points, particularly along either side of the superior sagittal sinus but to some extent along the other dural sinuses and sometimes in association with the middle meningeal vessels. It may be pointed out now that traction on most of these normal attachments which cross the subdural space produces pain.

The human dura is derived from paraxial mesoderm. According to Markowski,[3] the falx cerebri develops in two parts, an anterior part arising in the region of the crista galli and growing backward with the developing cerebral hemispheres, and a posterior part arising with the tentorium cerebelli. The tentorium develops as a growth of tissue from the region of the middle fossa on each side, extending backward until it surrounds the primitive mesencephalon. As the brain stem comes to lie more ventrally, the tentorium forms a definite septum separating the cerebrum and the cerebellum, with the incisura as its anterior edge. From the superior lamella of the tentorium the posterior part of the falx cerebri develops, growing forward between the two hemispheres and fusing with the anterior portion of the falx, as already mentioned.

THE DURAL NERVES IN MAN

Only a brief historical reference to the study of dural nerves will be made here, as a full account may be found in recent articles by Grzybowski [4] and Dowgjallo.[5] The seventeenth and eighteenth century anatomists Vieussens, Valsalva, Winslow and Pacchioni made mention of nerves in the dura, but their origin and distribution were not accurately studied until the nineteenth century. Arnold [6] (1851) described several recurrent branches of the trigeminal nerve to the dura, and illustrated these later in his beautiful atlas "Icones nervorum capitis" [7] (1860). At about the same period Luschka [8] was making similar studies of the dural nerves. Among others who contributed to the knowledge of these nerves during the nineteenth century, the names of Purkinje, Burgeri, Cruveilhier, Rüdinger and Nahmacher should be noted. The descriptions of the dural nerves given in most modern

3. Markowski, J.: Ueber die Entwicklung der Falx cerebri und des Tentorium cerebelli des Menschen mit Berücksichtigung ihrer venösen Sinus, Ztschr. f. d. ges. Anat. (pt. 1) **94**:395-439, 1931.

4. Grzybowski, J.: L'innervation de la dure-mère cranienne chez l'homme, Arch. d'anat., d'histol. et d'embryol. **14**:387-428, 1932.

5. Dowgjallo, N.: Ueber die Nerven der harten Hirnhaut des Menschen und einiger Säuger, Ztschr. f. d. ges. Anat. (pt. 1) **89**:453-466, 1929.

6. Arnold, F.: Handbuch der Anatomie des Menschen, Freiburg, A. Emmerling and Herder, 1851, vol. 2.

7. Arnold, F.: Icones nervorum capitis, Heidelberg, J. C. B. Mohr, 1860, plate 3.

8. von Luschka, H.: Die Nerven in der harten Hirnhaut, Tübingen, H. Laupp, 1850.

textbooks of anatomy are based on the pioneer work of Arnold and Luschka. Grzybowski has confirmed Arnold's earlier description of the dural nerves and their origins.

In order to analyze the physiologic mechanism of headache, we have restudied the nerve supply of the dura mater anatomically and have supplemented this study with a series of observations on neurosurgical patients.

Methods of Study.—The dural nerves were studied in man and in Macacus rhesus, and also in Macacus seven days after section. For macroscopic study fresh human dura (20 specimens) was obtained from the postmortem room. After removal of the brain in the usual manner, the entire dura was carefully stripped from the cranial cavity with the attached nerves and, whenever possible, with the sleeves from the bony foramens also. The crista galli and the cribriform plate were also removed with the dura.

The older methods of demonstrating the dural nerves by use of dilute acids or by staining with osmic acid were found to be less satisfactory than the following procedure:

The dura is washed thoroughly in running tap water to remove blood. It is then cut as desired and fixed for several days or longer in dilute solution of formaldehyde U. S. P. (1:10). The tissue is then washed for from five to ten minutes in tap water, immersed in a 20 per cent solution of silver nitrate and kept in the dark for twenty to thirty minutes. The pieces are again washed in running tap water for an hour or more, and rapid dissection of the cavernous sinus and the trigeminal ganglion is carried out under artificial light, with all daylight excluded. The dural nerves show clearly at this stage as dark brown threads against a white background of connective tissue. The plexus about the internal carotid artery within the cavernous sinus is also well stained.

After dissection and thorough washing out of the excess silver, the tissue is fixed in a 5 per cent solution of sodium hyposulfite, rewashed and dehydrated in two changes of 95 per cent and two changes of absolute alcohol. Thorough dehydration is essential. It is then cleared in methyl salicylate U. S. P. (2 changes). After this the nerves show as dark brown threads on a translucent background and can be studied carefully with a hand lens, by means of transmitted light and with the tissue immersed in a shallow dish of methyl salicylate. The best results are obtained with the dura of young adults, which is thin and strips easily from the bone.

In preparing the dura of Macacus rhesus the carotid arteries are injected with a 0.9 per cent solution of sodium chloride, followed by dilute solution of formaldehyde. U. S. P. (1:10). The brain is removed immediately after fixation and the dura stripped from the skull, as in man, and cut in suitable pieces, which are numbered with india ink, so that each piece can be identified later. The dura is stained in its entire thickness by the Gros-Bielschowsky method and is cleared and mounted in balsam. This allows one to trace most of the main nerve trunks through the dura from their origins. The finer nerve fibers within the tissue may or may not be completely impregnated. The same procedure has been used in studying the dural nerves of Macacus for evidence of degeneration.

For microscopic study of nerve fibers and nerve endings in the human dura the best results were obtained by the Gros-Bielschowsky method for frozen sections.

Dural Nerves in the Middle Fossa.—The middle fossa and the middle meningeal vessels are supplied mainly through branches arising from the second and third divisions of the trigeminal nerve. A branch of the third division, the nervus spinosus (first accurately described by Luschka in 1850), joins the middle meningeal artery outside the cranial cavity and reenters with the artery through the foramen spinosum along with the perivascular sympathetic plexus. At times this nerve runs directly from the third division to the artery without leaving the skull; there are usually other fine intracranial branches passing directly from the third division to the artery (*M. M.*, fig. 1). Sometimes these fibers from the third division constitute the entire trigeminal supply to the

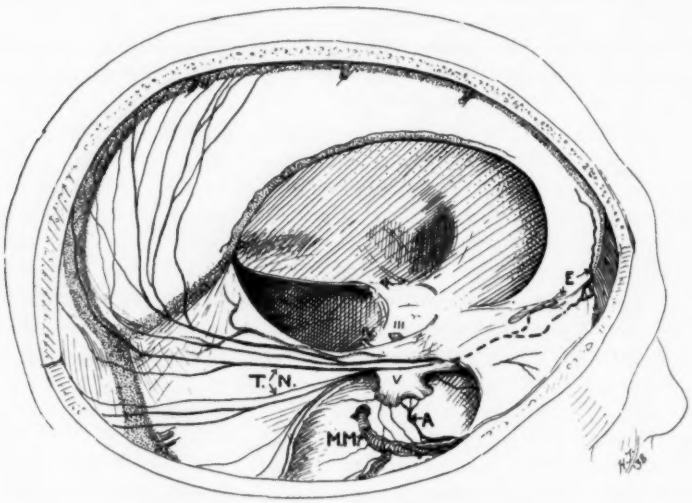

Fig. 1.—Drawing of the interior of the skull, showing the typical distribution of the dural nerves in the anterior and middle fossae on the right side. *M.M.* indicates the middle meningeal artery; *A*, the nervus meningeus medius; *T.N.*, tentorial nerves, and *E*, branches of the anterior and posterior ethmoid nerves to the falx and superior sagittal sinus.

middle fossa, but usually there are branches from the second division forming at least one well marked nerve strand, the nervus meningeus medius (or nervus recurrens rami secundi, described by Arnold in 1860). This nerve (or nerves) runs usually to join the anterior branch of the middle meningeal artery, although it may send fibers to both the anterior and the posterior branch (*A*, fig. 1). It may arise from the second division alone or from branches which appear to leave the ganglion from the angle between the first and the second or the second and the third division. A typical arrangement of these nerves in the middle fossa is shown in figure 2. Occasionally one or more fine nerves from

the first division join the anterior branch of the middle meningeal artery. In some cases a branch from the first division crosses the middle fossa without giving off any nerves to the middle meningeal artery, and runs

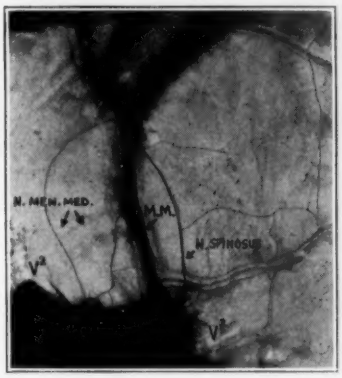

Fig. 2.—Photograph of the dura of the middle fossa in man. The second and third divisions of the trigeminal ganglion, *V 2* and *V 3*, are shown in the lower part of the picture. Branches to the middle meningeal artery (*M.M.*) are seen stained with silver nitrate, nervus spinosus (*N. spinosus*) coming from the third division and nervus meningeus medius (*N. men. med.*) from the angle between the second and the third division.

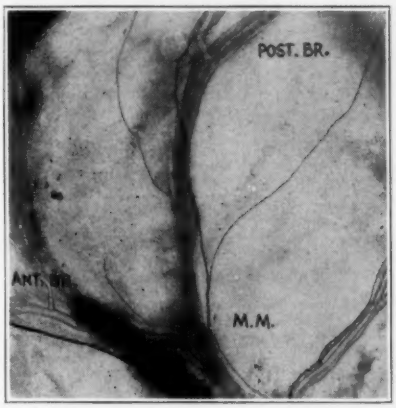

Fig. 3.—Photograph showing the abundant plexus, made up mainly of trigeminal fibers, which surrounds the larger branches of the middle meningeal artery (*M.M.*) in man. Several finer nerves are seen leaving the artery to be distributed in the dura. Silver nitrate preparation.

posteriorly into the tentorium, where it is distributed with branches of the tentorial nerve.

These nerves form an abundant plexus about the main branches of the middle meningeal artery, lying on the wall of the artery or on either side of the venae comites (fig. 3). They can be followed with the

smaller arteries over the convexity of the dura, but become finer and more difficult to trace as one approaches the superior sagittal sinus. Occasionally, a larger nerve can be followed to the edge of the sinus from this middle meningeal plexus.

While most of these nerves remain within the periarterial plexus, some may be traced elsewhere. A few nerves are seen leaving the arteries to branch in the dura itself within the middle fossa, as shown in figure 3. There may also be a fine twig from the nervus spinosus passing posteriorly to enter the hiatus canalis facialis, together with the superficial petrosal branch of the middle meningeal artery and the greater superficial petrosal nerve. This probably corresponds to the external petrosal nerve, and the present observations suggest that it is derived from the trigeminal nerve, rather than from the facial nerve or the sympathetic plexus on the middle meningeal artery, as stated in standard anatomic texts. One or more fair-sized nerves usually leave the middle meningeal plexus (sometimes accompanying a branch of the middle meningeal artery to the mastoid cells, called the superior tympanic artery) to enter other small foramens in the anterior surface of the petrous bone. According to Luschka, these supply the mastoid cells. Fine nerves can also be followed along the small branches of the middle meningeal artery which perforate the inner table of the overlying cranial bones.

In addition to branches of the trigeminal nerve, sympathetic fibers from the internal maxillary plexus (said to be derived mainly from the superior cervical ganglion) enter the skull with the middle meningeal artery and are distributed with its branches. In the dissections it was not possible to distinguish these from the trigeminal branches. The otic ganglion lies immediately below the foramen ovale, close to the middle meningeal artery, and receives sympathetic fibers from the middle meningeal plexus, as well as fibers from the glossopharyngeal nerve. It is not known whether the otic ganglion contributes any fibers to the dura through this meningeal plexus.

Sympathetic fibers also reach the dura by way of the internal carotid nerve and its periarterial plexuses. In dissections of the internal carotid and cavernous sympathetic plexuses a few fine nerves are seen, obviously running to the trigeminal ganglion and its divisions, and a few can be traced into the nearby dura, particularly between the first and the second division of the trigeminal nerve. However, no network of sympathetic and trigeminal fibers has been found about the trigeminal ganglion such as Dowgjallo [5] described, and from which all the dural nerves were said to take their origin. From macroscopic observations alone it is unlikely that these sympathetic fibers form more than a small proportion of the dural branches arising from the divisions of the trigeminal nerve, which have previously been described.

Older anatomic descriptions of the trigeminal nerve refer to branches from the trigeminal ganglion or its divisions which join the sympathetic plexus on the internal carotid artery. Hovelacque [9] mentioned several fine branches from the ganglion and from the ophthalmic division. In our gross dissections of the nerves in the cavernous sinus we have not observed any trigeminal branches to the carotid or the cavernous sympathetic plexus. In similar dissections of the cavernous sinus, Sheehan found connections between the trigeminal ganglion and the sympathetic plexus, but could not say from gross dissection whether these arose from the trigeminal nerve or the sympathetic plexus (Northfield [10]).

No definite branches have been seen leaving the greater superficial petrosal nerve (seventh cranial nerve) or the lesser superficial petrosal nerve (ninth cranial nerve) to enter the dura during their short course through the middle fossa. Chorobski and Penfield [11] suggested from their observations in monkeys that the greater superficial petrosal nerve may supply sensory fibers to the dura.

The innervation of the dura covering the sella turcica and forming the diaphragma sellae has not been carefully studied. It is said to receive sympathetic fibers from the plexus about the internal carotid artery.

Dural Nerves in the Anterior Fossa.—The dura of the anterior fossa contains a few perivascular nerves following branches of the middle meningeal artery. Some fine nerves are also seen in the dura close to the cribriform plate; they come from the anterior and posterior ethmoid nerves (branches of the first division of the trigeminal nerve [*E*, fig. 1]). The anterior ethmoid nerves also give off tiny branches which run up on either side of the superior sagittal sinus from its beginning at the crista galli, together with small arteries derived probably from the anterior meningeal artery.

The Tentorial Nerves.—The tentorium cerebelli, the dura of the parieto-occipital region, the falx and the adjacent sinuses are well supplied from each side by the nervus tentorii, a recurrent branch of the first trigeminal division, which is constant (*T. N.*, fig. 1). It was described by Arnold in 1826, although at that time he mistook it for a branch of the trochlear nerve. It takes its origin from the upper border of the ophthalmic division within the lateral wall of the cavernous sinus, about 1 cm. distal to the ganglion, and turns posteriorly to run in

9. Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du système grand sympathique chez l'homme, Paris, Gaston Doin, 1927.

10. Northfield, D. W. C.: Some Observations on Headache, Brain **61**:133-162, 1938.

11. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata with Observations on Pial and Intracerebral Vascular Plexus, Arch. Neurol. & Psychiat. **28**:1257-1289 (Dec.) 1932.

the sheath of the trochlear nerve, together with a sympathetic twig (Hovelacque [9]). It can be followed back close to the trochlear nerve, and in our observations did not appear to receive any fibers from it. On reaching the tentorium the tentorial nerves spread out fanwise between its layers, forming there an abundant plexus (fig. 4). As Grzybowski has described, these nerves may form several distinct groups within the tentorium but there is no constancy in their arrangement.

The tentorial nerves may be followed in numbers across the superior wall of the transverse sinus into the dura of the parieto-occipital region and the posterior third of the falx. They converge particularly toward the torcular region, whence they may be followed upward and forward in the walls of the superior sagittal sinus (superior longitudinal sinus) and the adjacent falx, sometimes as far as the midpoint of the falx (fig. 1). Beyond this point no nerves have been seen in the falx itself in gross dissections. Figure 5 shows how some of the larger branches

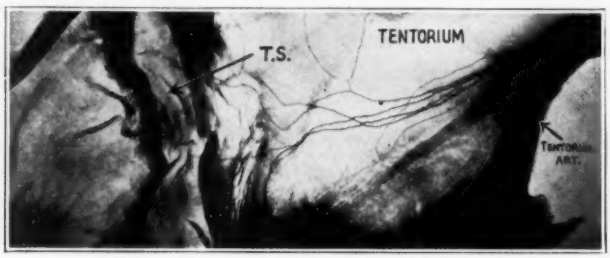

Fig. 4.—Photograph of the left half of the tentorium seen from above, showing the branches of the tentorial nerve in man. Some of these nerves can be traced in the superior wall of the transverse sinus (*T. S.*). Silver nitrate preparation.

(*T. N.*) may curve laterad and forward over the convexity of the dura to reach the parietal region, where they appear to join the plexus surrounding branches of the middle meningeal artery. The falx, being a midline structure, contains nerves which reach it from both halves of the tentorium. This rather complex course and distribution of the tentorial nerves are understandable when the embryologic development of the tentorium is kept in mind.

All the dural nerves which have been described can be traced to trigeminal divisions, but it is often impossible to follow them to their point of origin in the ganglion. Most of them seem to come from the lateral surface of the ganglion and its divisions. In Macacus rhesus, however, the thin layer of dura which covers the lateral surface of the ganglion allows these nerves to be followed, after staining, over the surface of the ganglion, and most of them seem to enter the part of the ganglion lying close to the origin of the first division. This suggests

that most of the dural nerves may have their true origin in the cells of the ophthalmic portion of the ganglion and only their peripheral origin from the second and third divisions.

Dural Nerves in the Posterior Fossa.—The nerve supply of the dura in the posterior fossa comes from the base of the skull. The most prominent are the recurrent meningeal branches of the vagus nerve, first described by Arnold and traced by him to cells of the jugular ganglion. Some of these fine nerves run up in the walls of the bulb of the jugular vein and the sigmoid sinus (*S*, fig. 5). One fairly constant nerve passes up from the jugular foramen and divides into several

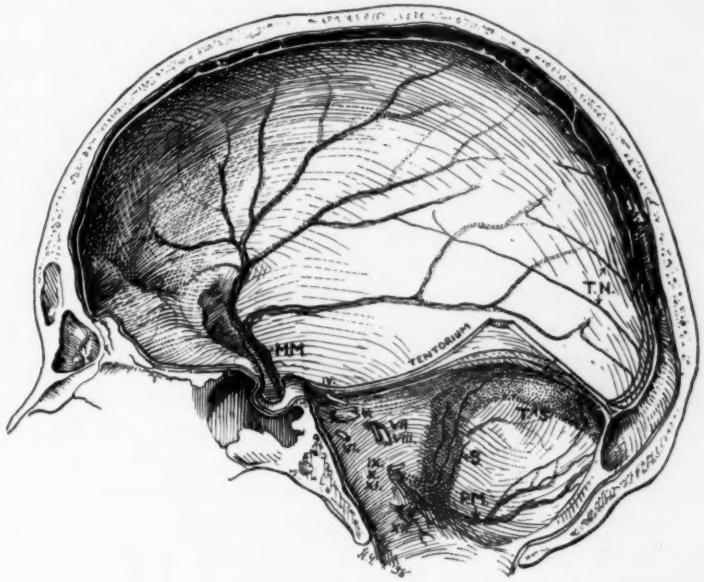

Fig. 5.—Drawing of the interior of the right side of the skull, after midline section in the sagittal plane. The falx has been removed. The drawing shows the distribution of nerves, with the middle meningeal artery (*M. M.*) over the convexity of the dura. Note the branches of the tentorial nerves (*T. N.*) extending forward into the parieto-occipital region. The meningeal branches of the vagus nerve may be seen passing backward from the jugular foramen. *T. S.* indicates the transverse sinus; *S*, the sigmoid sinus, and *P.M.*, the posterior meningeal artery.

branches, which may be associated with the posterior meningeal artery (*P. M.*, fig. 5) or may run quite separately from it. These branches can usually be followed to the inferior wall of the transverse sinus and the cerebellar falx, although an occasional branch may be traced in the posterior wall of the transverse sinus into the occipital region. The recurrent meningeal nerve lies rather close to the inner surface of the dura in places, so close that unless care is taken it may be brushed

off or torn during the removal of the brain or dura. It is usually difficult to trace all these dural nerves with certainty to their origin in the vagus trunk within the jugular foramen, where the vagus is closely associated with the glossopharyngeal and accessory nerves; it may be that some of the twigs are derived from the glossopharyngeal nerve, as stated by Stöhr.[12]

A few fine nerves are sometimes seen branching in the dura about the dural openings for the hypoglossal nerve. According to some anatomists these are hypoglossal fibers. Poirier, Charpy and Nicolas[13] described them as fibers from the lingual nerve which join the sheath of the hypoglossal nerve outside the skull and reenter by the hypoglossal canal to innervate the nearby dura and occipital sinuses. Hovelacque,[9] Piersol[14] and others quoted the description by Holl (1876), who claimed that these fibers consist mainly of branches from the upper two or three cervical roots which travel back in the hypoglossal sheath. It has not been possible in our dissections to establish the origin of the hypoglossal fibers to the dura, and we have not observed any other branches running directly from the cervical roots to supply the dura of the posterior fossa.

INNERVATION OF THE DURAL SINUSES

The superior sagittal sinus (superior longitudinal sinus) is supplied anteriorly by the branches of the anterior ethmoid nerve. Fine nerves also reach the sinus, particularly in its middle third, with the terminal branches of the middle meningeal artery. The posterior third of the sinus shows nerve fibers in great numbers derived from the tentorial nerve.

The inferior sagittal sinus (inferior longitudinal sinus) occasionally shows nerve fibers running in its walls, probably also derived from the tentorial nerve (fig. 1). Hovelacque[9] described branches of the first trigeminal division running to the walls of the cavernous sinus, but we have not observed any definite branches there.

The transverse (lateral), straight and superior petrosal sinuses are crossed by many branches of the tentorial nerve, while the superior petrosal sinus may also receive fibers from the third division of the trigeminal nerve or from the trigeminal ganglion itself.

The inferior wall of the transverse sinus and its continuation as the sigmoid sinus and the bulb of the jugular vein receive fibers from

12. Stöhr, P., Jr.: Mikroscopische Anatomie des vegetativen Nervensystems, Berlin, Julius Springer, 1928, p. 177.

13. Poirier, P.; Charpy, A., and Nicolas, A.: Traité d'anatomie humaine, Paris, Masson & Cie, 1921, vol. 3, pp. 316-318.

14. Piersol, G. A.: Human Anatomy, Philadelphia, J. B. Lippincott Company, 1907, vol. 2, p. 1277.

the vagus nerve, as already outlined, with possibly a few twigs from the ninth and twelfth nerves. It will be pointed out later that section of the trigeminal nerve renders the upper leaf of the transverse sinus insensitive, suggesting that no sensory fibers of the vagus nerve penetrate to the upper surface of this sinus. The innervation of the inferior petrosal and the basilar sinuses has not been established.

In man nerve fibers are frequently observed in the walls of the subdural portions of the cerebral veins, that is, in those portions which lie in the subdural space before entering a dural sinus. These fibers are probably of dural origin. The vein of Galen is also surrounded by nerve fibers, the origin of which is uncertain, although some of them may come from the tentorial nerves.

DURAL NERVES OF MACACUS RHESUS

Little need be added with regard to the nerve distribution in the dura of Macacus rhesus, as it resembles closely the arrangement in man already described. Trigeminal branches to the middle fossa are numerous, but show no constant arrangement. As mentioned before, most of them can be seen leaving the ophthalmic part of the trigeminal ganglion and streaming across its lateral surface to enter the middle fossa. They join the meningeal vessels and are distributed with them, giving off fine branches to the arterial walls and occasionally to the dura. The tentorial branch shows an origin and distribution similar to those of the tentorial nerve in man. No branch of the greater superficial petrosal nerve to the middle fossa has been observed. In the posterior fossa fine nerve trunks are constantly seen in the walls of the sigmoid sinus. While these have not been followed to their origin, they probably correspond to the recurrent branches of the vagus nerve described in man. Some fibers appear to run up through the foramen magnum to the dura covering the basiocciput, in continuity with an abundant nerve plexus which is present in the spinal dura and which is derived from the roots of the spinal nerves. A few fibers have been seen in the dura of the posterior fossa around the opening for the abducens nerve.

The superior sagittal sinus receives in its posterior third an abundance of nerve fibers from the nervus tentorii of either side. In its middle third nerve fibers are observed on either side of the wall of the sinus, many of which reach it with terminal branches of the middle meningeal artery. Two strands of nerve fibers are usually seen running parallel to the sinus, together with a small artery. These lie on either side of the midline, at the angle between the lateral and the superior wall of the sinus. These nerve strands are continuous anteriorly with small nerves reaching the sinus at its anterior end, derived from the anterior ethmoid nerves. Nerves are often seen crossing the midline in the

superior wall of the sinus. Nerves are also abundant in the superior wall of the transverse and the straight sinus—branches of the tentorial nerves.

The effect of destruction of the trigeminal ganglion on the dural innervation in Macacus has also been observed. In our procedure the ganglion is approached by a subtemporal craniotomy. A small dural incision is made, and the temporal lobe is retracted upward. In this way the ganglion can be visualized clearly through the translucent dura, lying against the medial wall of the middle fossa. The ganglion is then destroyed slowly by electrocoagulation. It is impossible to avoid damage to the sympathetic fibers to the dura in destroying the ganglion or its branches, so that one actually studies the effect of destruction of both the trigeminal and the sympathetic nerve supply.

Study of the dura, after seven days was allowed for degeneration of the peripheral branches of the trigeminal nerve to take place, showed undoubted signs of degeneration of all nerves in the dura of the anterior and middle fossae of the same side and of the perivascular nerves about all branches of the middle meningeal artery over the dural convexity. The tentorial nerve of the same side and, as would be expected, about half the fibers seen in the falx (posterior third) were also degenerating. Similar degenerated fibers were seen in the walls of the superior sagittal sinus throughout its length, mainly on the side of operation, although a few were present on the other side of the midline, indicating that there is slight overlapping of the nerve supply.

Degenerating fibers could also be seen in the walls of veins entering the superior sagittal sinus and in the vein of Galen, close to its junction with the straight sinus. It was seldom that any degeneration was observed in nerves of the posterior fossa below the level of the transverse sinus. Except for the slight overlapping of fibers on the superior sagittal sinus, no signs of degeneration appeared in the nerves in the dura of the opposite side.

In several animals the dura was studied for signs of degeneration of nerves following removal of the superior cervical ganglion, but the results were inconclusive. Chorobski and Penfield,[11] using a similar method, were unable to demonstrate degeneration of pial perivascular nerves, and suggested that the lack of degeneration is due to scattered sympathetic ganglia distal to the superior cervical ganglion.

STRUCTURE OF DURAL NERVES AND NERVE ENDINGS

The dural nerves of man and Macacus are both myelinated and unmyelinated. In osmic acid preparations of the human dura, taken from the region of the middle meningeal artery and cut transversely, many well myelinated fibers of various sizes were seen in the dural nerve

bundles (fig. 6). Accurate fiber counts were not made, but most of the fibers ranged from 2 to 4.5 microns in diameter, with an occasional larger fiber. A further study of the structure of the dural nerves is in progress.

It has been seen from our dissections that the nerves tend to be distributed about blood vessels and along the large venous sinuses, with a few nerves branching off into the dura itself, where they are soon lost from view. The nerves entering the petrous bone are presumably sensory fibers destined for the mastoid cells and the middle ear. The main dural supply seems to be made up of nerves containing vasomotor

Fig. 6.—Cross section of a nerve bundle in the dura, lying close to a middle meningeal vein. Osmic acid stain.

(sympathetic) fibers for the meningeal arteries, together with many sensory (trigeminal, vagus and other) fibers which probably end in, or close to, the walls of meningeal vessels and sinuses. The nervi proprii, or nerves of the dura itself, which probably end within the dural connective tissue, seem much fewer and are most commonly seen in the dura near the base and in the tentorium and posterior part of the falx.

Nerve endings in the human dura and on dural vessels are difficult to demonstrate, though nerve endings are seen frequently on blood vessels elsewhere in the body. In the meningeal arteries, Traum [15]

15. Traum, E.: Beiträge zur Innervation der Dura mater cerebri, Ztschr. f. d. ges. Anat. (pt. 1) **77**:488-492, 1925.

observed nerve fibers branching within the muscular coat but could not find sensory end organs or ganglion cells within the walls of the vessels. More recently, Dowgjallo[16] has described several types of sensory endings in the adventitia, using methylthionine chloride (methylene blue) methods.

Within the dura itself the nerve endings are sparse. Traum observed myelinated fibers ending in fine unmyelinated arborizations—sometimes with tiny end bulbs or knoblike swellings (figure **7** illustrates this branching type of ending). Dowgjallo observed within the dura nerve plexuses with fine varicose endings lying close to the inner surface of the dura. Except for the pacinian corpuscles in the dura mentioned

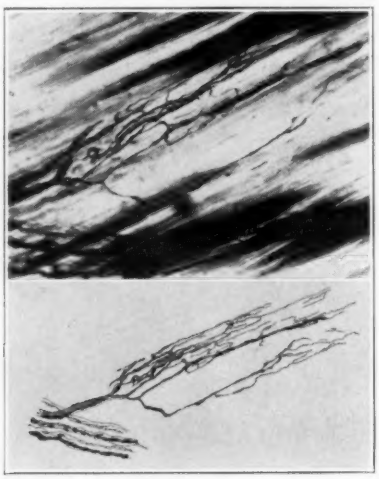

Fig. 7.—Branching nerve ending from the human dura at the base of the skull. Gros-Bielschowsky method. Below is a camera lucida drawing of the same nerve ending.

early by Krause (cited by Henle[17]), no encapsulated endings have been demonstrated in the human dura.

In this study no definite endings were found in the human dura except for the branching type we have illustrated here. No endings were seen in the walls of the sinuses, with the Gros-Bielschowsky technic. In Macacus several types of encapsulated endings were seen in the dura of the posterior fossa (fig. 8 *A* and *B*), as well as fine arborizations within the dural connective tissue elsewhere.

16. Dowgjallo, N.: Beiträge zur Lehre von der Innervation des peripherischen Blutgefäss-systems, Ztschr. f. d. ges. Anat. (pt. 1) **97**:9-54, 1932.

17. Henle, F. G. J.: Handbuch der systematischen Anatomie des Menschen, Brunswick, F. Vieweg u. Sohn, 1871, vol. 3, pt. 2, p. 404.

The dural nerves in man are somewhat variable in their mode of origin and distribution, particularly those in the middle fossa. We have described their usual arrangement. In any individual case the arrangement of the nerves is not necessarily the same on the two sides. There also seem to be genuine differences in the number of dural nerves from case to case. Occasionally no nerves can be demonstrated in the dura of the posterior fossa, though this may be due only to faulty staining.

In summary, it may be stated that the trigeminal nerve supplies the cerebral dura everywhere except in the posterior cranial fossa. The middle meningeal arteries carry with them fibers which emerge from the ganglion with the second and third divisions, and less constantly with the first division. The superior sagittal (or longitudinal) sinus is supplied mainly from the first division of the trigeminal nerve (through

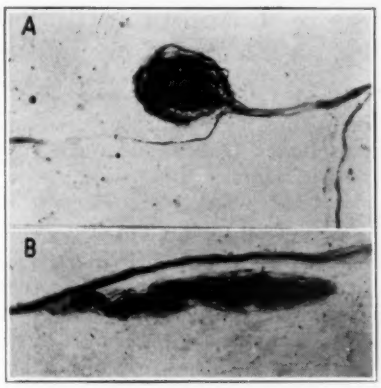

Fig. 8.—Encapsulated (unsectioned) nerve endings from the dura in the posterior fossa (Macacus rhesus). Gros-Bielschowsky method. The nerve ending in *B* closely resembles a pacinian corpuscle.

the nervus tentorii and a branch of the anterior ethmoid nerve from each side). Other fibers may reach it with branches of the middle meningeal artery which approach the midline. The transverse sinus (superior wall) is supplied by the tentorial nerve. The inferior wall of the transverse sinus and the dura of the posterior fossa are supplied by the tenth cranial nerve and smaller branches arising possibly from the ninth and twelfth cranial nerves. Branches from the upper cervical nerves have not been demonstrated. In addition, there are sympathetic perivascular fibers in the dura.

SENSITIVITY OF INTRACRANIAL STRUCTURES

That the human dura is sensitive in certain regions has long been known from the observations of Krause, Cushing and other neuro-

surgeons. Foerster [18] reported that the dura was sensitive particularly at the base of the skull and close to larger branches of the middle meningeal artery, while the dura of the convexity was less sensitive. The tentorium he also found very sensitive, but not the pia or the brain substance. Traction on larger cerebral vessels during removal of brain tissue he reported as sometimes producing pain. The choroid plexuses were also found to be sensitive.

Lennander [19] (1906) and, later, Neiding [20] stated that the dura, apart from the meningeal arteries, was practically insensitive, but their observations were made on limited areas.

In 1934, one of us (W. P.[21]) reported his observations on the sensitivity of the dura and other intracranial structures, made during the course of exploratory operations performed with local anesthesia, and discussed their significance in relation to mechanisms of headache. These observations may be summarized and amplified here. Northfield [10] has made similar, but less detailed, observations.

Cerebral Veins and Arteries.—Electrical stimulation of the middle cerebral artery near the circle of Willis may produce pain in the ipsilateral temporal region or above the ipsilateral eye. Arteries elsewhere in the cortex are rarely found to be sensitive. This is contrary to the statement of Spriggs [22] that "the most sensitive areas are close to the vessels in the pia mater."

Cerebral Tissue.—The tissue of the brain is itself insensitive, although several apparent exceptions have been observed in which electrical stimulation of the intact pia mater (apart from the larger blood vessels) produced pain on the same side of the head (Penfield and Boldrey [23]). It is possible that in some of these cases the pain was caused by spread of the electric current to nearby sensitive dural veins or sinus walls. Manipulation and electrical stimulation of the fissure of Sylvius sometimes produce ipsilateral pain. At times this clearly arises from attached veins.

In 1 case, with the use of local anesthesia, the foramen of Monro was retracted strongly without sensation. The thalamus was pressed on from within the ventricle with no sensation whatever. In 2 cases the choroid plexus of the lateral ventricle, when stimulated both by direct pressure and by galvanic current, was found to be completely insensitive.

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18. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Berlin, Urban & Schwarzenberg, 1927, pp. 10-11.

19. Lennander, K. G.: Ueber lokale Anästhesie und über Sensibilität in Organ und Gewebe; weitere Beobachtungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **15**:465-494, 1906.

20. Neiding, M.: Zur Frage nach der Sensibilität der Dura mater des Gehirns, Deutsche med. Wchnschr. **53**:795-796, 1927.

21. Penfield, W.: A Contribution to the Mechanism of Intracranial Pain, A. Research Nerv. & Ment. Dis., Proc. (1934) **15**:399-416, 1935.

22. Spriggs, E.: A Clinical Study of Headaches, Lancet **2**:1 and 63, 1935.

23. Penfield, W., and Boldrey, E.: Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**:389-433, 1937.

Meningocerebral Scars.—Such scars are usually insensitive, but old scars, particularly in the temporal lobe, may be sensitive and may continue to be so even after the dura is dissected from its attachment, an indication that under these circumstances sensory nerves may leave the scar by another route to travel centrally through the brain itself or, more probably, along the cerebral vessels.

The Dura.—After removal of the bone flap the dura itself is generally insensitive, except at points where branches of the middle meningeal artery are present. Pressure or electrical stimulation of the middle meningeal artery or its branches causes sharp pain which is well localized to the area of stimulation or is referred to the ipsilateral temporal region. In 2 cases the pain was referred to the face or near the back of the lower jaw, but this is exceptional. Occasionally, even the meningeal artery proves to be insensitive. Injection of procaine hydrochloride about the middle meningeal artery usually renders the whole temporoparietal region of the dura insensitive. However, after a large parietal flap of dura has been cut, sensitive points are frequently found in the dura at the mesial edges of the

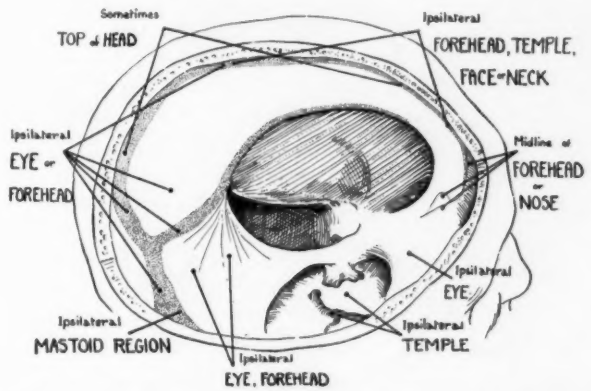

Fig. 9.—This drawing indicates the areas of the cerebral dura which are usually found to be sensitive at operation and the localization of the pain which is produced.

opening, particularly near small arteries. This observation indicates that there must be some innervation of the dural convexity from the midline and from occipital and frontal sources, in addition to the middle meningeal plexus, and the anatomic description already given tends to confirm it.

The dura of the parietal, temporal and occipital regions is generally more sensitive than that of the frontal region. When the intact dura has been stimulated by pressure on its inner surface by means of a curved instrument inserted through a trephine hole into the subdural space, the patient has usually localized the pain close to the point of stimulation. It is assumed that when pain is produced pressure is usually being exerted in the region of a small branch of the meningeal artery. In the posterior fossa, pressure on the dura of the floor in the vicinity of the jugular foramen produces pain in the ipsilateral mastoid and cervical regions.

Walls of the Dural Sinuses.—The walls of the sinuses, and sometimes the large veins entering the sinuses, are found to be extremely sensitive. Pain produced from the dural sinuses, like that arising from pressure on the falx and tentorium, is apt to be referred to a distance. The localization of this referred pain varies somewhat from one patient to another but the usual direction of reference is that indicated in figure 9.

Stimulation of the lateral aspect of the superior sagittal (superior longitudinal) sinus in its posterior third causes pain which is usually referred behind the ipsilateral eye or to the forehead. Pain with the same reference is produced from the lateral wall of the straight and the upper wall of the transverse sinus. Stimulation of the most lateral portion of the transverse sinus may produce pain referred to the ipsilateral mastoid region.

Stimulation of the superior sagittal sinus in the vicinity of the crista galli causes pain in the brow or nose. Location of pain referred from the anterior two thirds of the superior sagittal sinus is more variable. The pain is ipsilateral and may be felt in the forehead, in the temple or occasionally in the region of the ear and radiating downward into the neck. It is sometimes referred to the top of the head. In any given person the site of the referred pain is usually constant.

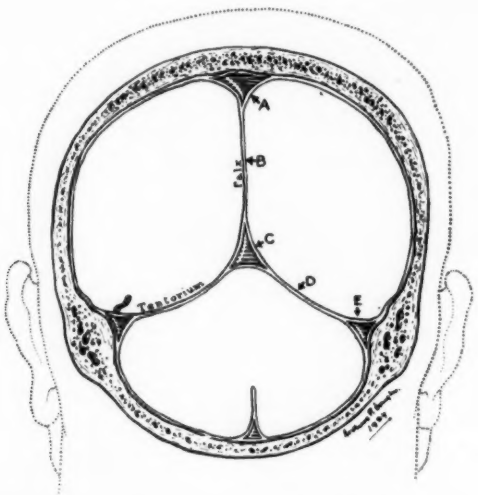

Fig. 10.—Schematic coronal section through the head to indicate the relation of the falx, tentorium and dural sinuses. It is obvious that pressure on the falx or the tentorium at *B* or *D* is apt to stretch the sensitive area of the adjacent wall of the superior sagittal sinus (*A*), the straight sinus (*C*) or the transverse sinus (*E*). From Penfield.[21]

Pressure or traction on veins entering the sinuses or traction on pacchionian granulations or on the portion of the falx or tentorium adjacent to the sinuses causes pain similar to that produced by stimulating the walls of the sinuses.

Falx and Tentorium.—The falx is found to be most sensitive in its posterior third. Gentle lateral pressure on the falx usually causes pain to be referred to the same side of the head. That this should be so is obvious when the structure of the sinuses is considered, as shown in figure 10. Pressure at *B* causes traction on the wall of the sinus on that side, not on the contralateral wall. The same applies to the tentorium, as downward pressure at *D* stimulates only one wall of the straight and the transverse sinus, at *C* and *E*. Upward pressure would stretch the other walls, with a different reference of pain.

In one case pressure on the free margin of the falx, in its middle portion, caused pain which was referred behind the ipsilateral eye. In another case electrical stimulation in the same region, without pressure, produced pain in both temples, and in a third case the pain on electrical stimulation in this area was said to be in the middle of the head.

Pressure downward on the tentorium will cause pain to be referred to the frontal region on the same side. Electrical stimulation of the tentorium may cause pain of similar character which is referred to the same region or behind the eye. Pressure upward on the tentorium or on the under surface of the transverse sinus probably produces pain referred to the suboccipital region and down the back of the neck, but our observations here are too few to permit generalization with certainty.

Character of Pain.—The sinuses are sensitive to stimulation by pressure, traction, heat and electricity. All these forms of stimulation produce the same form of sensation, i. e., pain which is described by the patient as sharp or pressing, or as "headache." The pain resulting from stimulation of the meningeal arteries is usually sharp and well localized.

Objection might be made that the references of pain as recorded here are mistakes in localization due to the anesthesia of the scalp and to the presence of a large craniotomy opening with displacement of tissues from their normal position. Similar references have been found when the dura and dural sinuses were stimulated through small trephine openings; so this objection is not valid.

Autonomic Reflexes.—On a number of occasions, pressure, traction or other manipulation of the superior sagittal sinus under local anesthesia has produced sudden nausea, sometimes followed by yawning, restlessness and vomiting. Such initial manipulation is, of course, usually associated with pain. There may also be an abrupt fall of blood pressure, as was noted in case 5.

DURAL SENSITIVITY AFTER SECTION OR BLOCK OF THE TRIGEMINAL NERVE

In addition to these observations on the sensitivity of the dura with its nerve supply intact, the results of exposure and stimulation of the dura were determined in the following cases in which the fifth nerve had been previously interrupted.

CASE 1.—I. H., a woman aged 54, had had complete section of the posterior root of the left trigeminal nerve two years before for atypical neuralgia of the left side of the face, without relief.

The left subdural space was explored at several points through trephine openings. The dura was opened beneath each trephine hole and pressure exerted on the inner surface of the dura with a curved instrument, thus squeezing the dura between the instrument and the bone. It caused no pain. Ordinary pressure on the falx and the superior sagittal sinus produced no pain. Heavy pressure on the falx produced pain, which was referred to the *right* side of her head only. Strong pressure and faradic stimulation of the left side of the superior sagittal sinus repeatedly gave pain referred to the *right* side of her head only. Pressure on the left side of the tentorium gave no pain.

At a later time the left posterior fossa of the same patient was explored through a suboccipital craniotomy, with local anesthesia. Pain was then produced

by pressure on the floor of the fossa. The pain was felt in the left side of her jaw and throat and seemed to be identical in character and location with her habitual pain.

CASE 2.—H. W., a man aged 61, had had complete section of the posterior root of the right trigeminal nerve for facial pain fourteen months previously, but without relief. A diagnosis of atypical facial neuralgia was made. The right subdural space was exposed at several points through trephine openings. The following is quoted from the operative note: "The tentorium on the right side may be taken to be insensitive. The transverse sinus was completely insensitive; the straight sinus was almost insensitive, but strong pressure here produced mild pain on the opposite (*left*) side of the head. The posterior part of the superior sagittal sinus seemed to be insensitive to pressure. Pressure on the falx, however, at one or two points posteriorly produced pain on the *left* side; anteriorly, there was sensation from the dura just to the right of the falx which was all referred to a point above the *left* eye or in that eye. There was no evidence that we reproduced the patient's habitual pain."

In a third case the dura was stimulated after injection of nupercaine into the trigeminal ganglion. Under these circumstances, the sympathetic branches to the middle meningeal artery were probably still functioning, in contrast to the condition in cases 1 and 2, in which the middle meningeal artery had been tied.

CASE 3.—W. K., a man aged 25, was operated on by one of us (W. P.) in 1934, and a right frontal meningocerebral cicatrix was excised. At the time of operation it was noted that he had pain above the right eye, or referred to the right temple, from manipulation near the superior sagittal sinus in the frontal region. Manipulation of the falx itself caused pain which was regularly and definitely referred to the right temple. In May 1939 a second craniotomy was done in the same region, with removal of more scar tissue. On the day before the second operation, wire leads were inserted beneath the bone flap for electrographic studies, and it was then noted that the dura was very sensitive.

Immediately preceding the second craniotomy a 1:1,500 solution of nupercaine was injected into the right trigeminal ganglion through the foramen ovale, producing complete sensory loss over the cutaneous area of the right trigeminal nerve and abolishing the right corneal reflex. The usual infiltration anesthesia was used in the scalp, and the bone flap was reelevated. Mechanical stimulation of the exposed dura did not produce pain except near the midline, where stimulation of the superior sagittal sinus at two points caused pain, which was always felt to the *left* of the midline. As the analgesia of the forehead began to wear off and the right corneal reflex reappeared, it was found that the dura was sensitive in the temporal region, the pain being felt in the temple. At this time there was still complete analgesia over the face in the area supplied by the second and third divisions.

The patient, who was an accurate and intelligent observer, later remarked that his second operation had been much less painful than his first, even though the fifth nerve did not remain completely blocked throughout the operation.

In cases 1 and 2 it is evident that complete unilateral section of the fifth nerve produced complete ipsilateral anesthesia of the dura above

the tentorium, including the upper wall of the transverse sinus and half the tentorium. Such section did not render the dura of the posterior fossa insensitive. Each side of the superior sagittal and straight sinuses must be innervated almost exclusively by the trigeminal nerve of that side. In case 3 the dura appeared completely insensitive in the area tested in the frontotemporal region, as long as the fifth nerve remained completely blocked. Strong stimulation near the midline caused pain which was felt only in the intact, or the opposite, side, as in cases 1 and 2.

In the following case the dura was stimulated after *partial* section of the posterior root, and the findings in this case may be mentioned briefly.

CASE 4.—A. G., a woman aged 54, had chronic pain localized in the left side of the lower jaw and behind the left mastoid area. About a year previous to our study of her case, the posterior roots of the second to the fourth cervical nerve had been severed on the left side, and a subtotal posterior root section of the trigeminal nerve had been performed by the temporal approach, fibers of the third division only being sectioned. The middle meningeal artery was probably ligated at that time. There was no relief from pain. Exploration of the left subdural space in the frontoparietal region, with stimulation of dural structures, was carried out under local anesthesia. Pressure on the left middle meningeal artery gave the characteristic reference of pain to the left temple. Pressure on the superior sagittal sinus at different points caused pain in the left eye and the left temple, and sometimes in the region of the left ear. With firmer pressure on the sinus or the falx pain was felt in the temple or eye on the *right* side as well as on the left. These observations would indicate that section of fibers of the third division only (in the posterior root) together with ligation of the middle meningeal artery does not permanently affect the sensitivity of dural structures.

Contralateral reference of pain is seldom observed on unilateral stimulation of the falx or the superior sagittal sinus when both trigeminal nerves are intact, probably because a stronger mechanical or electrical stimulus is usually required—a strength of stimulus which the patient without nerve section would not tolerate because of ipsilateral pain. In cases of habitual unilateral pain, however, the threshold for producing pain on the habitual side of reference from the superior sagittal sinus may be lower than that for pain on the other side, as in case 5, to be described.

DURAL HEADACHE AND "ATYPICAL TRIGEMINAL NEURALGIA"

We shall now report 3 cases of chronic pain in the head and face in which we consider that the pain was of dural origin. They illustrate the application of the anatomic facts already described.

CASE 5.—*History.*—M. M., a woman aged 55, complained of dull, steady pain centering in front of the left ear and extending into the left side of the neck, which had previously been diagnosed as atypical trigeminal neuralgia.

Beginning at the age of 19, she had had pain over the left eye, which was darting in character. At the age of 34 the pain over the left eye had become severe, and she started on a career of neurectomies. The supraorbital nerve was cut peripherally, which gave relief for a short time, but the pain reappeared and moved downward in the face. At the age of 41 an operation was carried out on the gasserian ganglion, which brought relief for two years, but the operation was followed shortly by complete paralysis of the left facial nerve. Anesthesia in the area supplied by the trigeminal nerve was complete for a time after this operation, but only the third division remained permanently numb. When the pain returned, it was located above and behind the left ear, and there appeared curious spasms of the base of the tongue on the left, which made chewing and swallowing difficult. The spasms were considered to be pseudomotor phenomena due to abnormal activity of parasympathetic fibers from the chorda tympani nerve which entered that side of the tongue through the otherwise paralyzed lingual nerve. The condition was partially relieved by section of the lingual nerve (Cobb and Mixter [24]). There were also at that time edema and redness over the left malar bone, as though hyperirritability of the vascular system existed in the denervated area of the cheek.

At the age of 49, left cervicothoracic sympathectomy, including removal of the stellate ganglion, was carried out, which produced temporary improvement. At 53, the second, third and fourth cervical nerves were sectioned, and this again brought relief; at the age of 54, however, pain returned in the face and neck, focusing chiefly in the jaw, anterior to the left ear. This was her complaint when she consulted us, at the age of 55.

She was a highly strung, despondent woman, obviously suffering dull pain, which became intense at intervals. Her face and neck presented an irregular pattern of postoperative sensory changes. The skin supplied by the second division of the trigeminal nerve was partly hypalgesic; the area of distribution of the third division, including the tongue, was analgesic; parts of the second, third and fourth cervical segments of the skin on the left side were hypalgesic and part of the second was hyperalgesic. Sweating was absent in the left side of the face, and there was partial paralysis on this side of the face.

There was some deviation of the nasal septum to the left, but injection into the left sphenopalatine ganglion gave no relief. There was moderate malocclusion of the jaws, but correction of the "bite" gave no relief. There was moderately increased calcification on the under surface of the left frontal bone.

The most likely explanation for this curious migration of pain, with temporary relief by nerve section, seemed to be that the pain was referred from some primary undiscovered focus. It had been our experience that patients sometimes complained of pain in the same side of the face and neck when the superior sagittal sinus or falx was stimulated; therefore, mindful of the calcification of the left frontal bone, we determined on exploration of the dura on that side.

Operation.—On April 25, 1936, with the use of local analgesia, two trephine holes were made in the left frontal bone, without opening the dura. Through the first hole near the midline a curved instrument was inserted between the bone and the dura, and pressure was exerted on the dura. With stimulation in several directions no sensation was produced, but pressure near the superior sagittal sinus at one point caused the patient to cry out with pain and to say that it was like her habitual pain, localized in the left side of the face and neck.

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24. Cobb, S., and Mixter, W. J.: Lingual Spasm, Ann. Surg. **101**:49-55, 1935.

Consequently, the scalp (*S*) was reflected forward and and a small osteoplastic bone flap (*O*) turned laterad on the temporal muscle, as seen in figure 11, in which *1* lies on the dura at the point where the first trephine hole had been made; *2* lies on the superior sagittal sinus. Stimulation at that point, i. e., directly over the sinus, with a faradic current produced pain referred to the left eye, the left side of the face and the left ear. The under surface of the bone flap bore a whitish bony elevation, which had been seen in the roentgenograms. Two small defects were present in the dura immediately beneath this enostosis. Otherwise the dura appeared normal.

After the dura was opened, the brain appeared essentially normal for a person of the patient's age. Beneath the dura, at point 1 (fig. 11), were seen two

Fig. 11 (case 5).—Photograph made at operation, after reflecting the scalp (*S*) forward and turning a small left frontal bone flap (*O*) laterad. The dura has not been incised. *1* indicates the position of the first trephine hole, and *2* the position of the superior sagittal sinus. At *3*, above and lateral to the orbit, pressure on the dura caused pain which was felt above the eye.

veins that entered the superior sagittal sinus. Cutting these veins caused pain, but after section the portion of the veins remaining on the hemisphere was insensitive. From this point forward the sinus was sensitive to pressure or electrical stimulation, and the pain was of the habitual type and was referred to the left side of the face and down the left side of the neck.

The falx itself seemed to be tense, and pressure on it, between *A* and *B* (fig. 12), produced pain with the same reference as had pressure on the sinus. There were several holes in the falx, especially posteriorly, through which the two

cerebral hemispheres were adherent, and it was noted that the mesial surface of the right frontal lobe was yellowish. At a point about 4 cm. above the crista galli, the falx was slightly thickened (at *C*, fig. 12) and presented a ridge of connective tissue like the crossing fibers of a scar. This area was very sensitive.

The left frontal lobe was retracted from the falx. Nupercaine was then injected into the falx, between its two layers, at a site just below the thickening *C*, without the patient being informed of what was being done. In a moment she remarked with surprise "my steady pain is gone." It was then found that the superior sagittal sinus adjacent and posterior to the injection had become insensitive. That portion of the falx that lies between the dotted lines in figure 12 was then removed, including the superior sagittal sinus. The removal was begun posteriorly, and the manipulations were now painless until the anterior incision was made.

Without realizing that the falx was still sensitive at its attachment to the crista galli, the operator cut it across quickly at this level. This produced a sudden severe bout of the old pain and an alarming alteration in the patient's

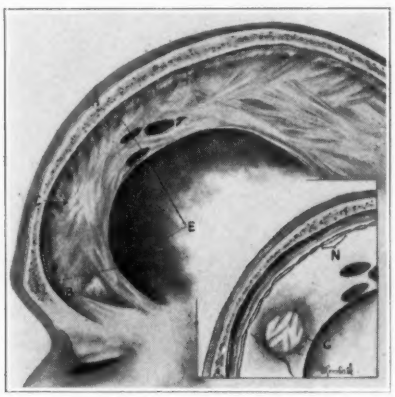

Fig. 12 (case 5).—In this drawing the anterior part of the falx, *C* indicates the thickened area above the crista galli, and the dotted lines show the area of falx resected. The distribution of the nerves in this section of the falx is shown in the smaller figure, schematically.

condition. The anesthetist reported that she could not feel the patient's pulse or read her blood pressure. Injections of caffeine and epinephrine were given quickly, and the head of the table was lowered. The blood pressure returned from 0 to 30 mm. systolic and then to 40 mm. The patient vomited and seemed anxious. A second injection of epinephrine was given, and the pressure came back quickly to 100 mm. It was obvious that the afferent sensory pathway passed downward and forward along the falx and sinus, in fact, along the course of the ethmoid nerves. It was also apparent that it had been the sudden stimulation of these nerves that had produced such an overwhelming autonomic effect, as well as pain.

Certain other observations which were made with regard to pain mechanisms during the operation should be recorded. Pressure on the unopened dura, at *3* (fig. 11), which was lateral to and above the orbit, produced pain referred locally above the eye. When the one branch of the middle meningeal artery

was tied pain was felt locally near the lateral angle of the left eye. Ligation of the other branch did not produce pain. Thus, pain due to stimulation of the convexity of the dura wherever sensitivity remained was local and was not referred. Adhesions between the hemispheres were not sensitive.

Curiously, stimulation of the right side of the superior sagittal sinus by pressure produced pain on the left side of the face at first. This stopped after anesthetization of the falx. Then strong stimulation on the right side of the sinus produced local pain anteriorly on the right. Thus, the pain referred to the left side of the face depended on the anterior ethmoid nerves in the falx and sinus, and these nerves produced pain referred to the left only. There was still innervation to the right side of the sinus by the middle meningeal fibers, which gave less severe pain, with a higher threshold on the right side.

Course.—At the time of removal of the falx the patient's neuralgia disappeared, and there has been no suggestion of it in the three and one-half years that have elapsed since operation. She has noticed a marked decrease in nervous tension also and has become a more placid, normal person, possibly as a result of the abolition of afferent impulses along the pathway, section of which produced so spectacular an effect on the autonomic nervous system.

The piece of falx which was removed was found to have nerve fibers within it, usually perivascular in position and most numerous on the superior sagittal sinus (*N* in inset of figure 12). There was also a small artery on the falx, shown in the inset, which carried nerve fibers up to the region of the cicatrix *C*.

The pain in this case was due to the presence in the falx of a contracting, painful scar. Pain appeared first at the age of 19, and there was no history of injury after the time of birth. Delivery was difficult, and it may well have resulted in tearing the falx so as to produce the defects and the thickening. Adhesion of the two hemispheres through the falcial defects, and particularly the yellowish discoloration of the adjacent pia mater, lend support to this supposition.

The gradual contraction of the thickened area (*C*, fig. 12) may have produced the unusual tenseness of the falx, which is one of the few drum-like structures in the body incapable of yielding quickly to cicatricial pull. This unrelieved tension on the anterior portion of the falx is proposed as the true source of the pain in this case, the immediate afferent nerves being the ethmoid branches of the first division of the trigeminal nerve.

At all events, the facts are these: The falx was tense; the thickening was hypersensitive, with typical reference of pain; blocking its nerve supply arrested the pain, and removal of the area in question gave permanent relief. It should be added that during operation pain produced from other structures was never referred to the jaw or neck and that the patient had no information of what area was being stimulated at any time.

The pain was of the referred type, to the left side of the face and neck. It is true of such pain in general that it may be relieved by operation on the peripheral nerves to the area of skin to which the pain is

referred (as in cases of angina pectoris). Such relief is apt to be temporary, and the pain may spread into more distant areas as long as the primary focus remains. This seems to be the only explanation of the patient's temporary relief from the previous peripheral neurectomies. If anesthesia had been permanent in the first division after the operation on the gasserian ganglion, relief might have been permanent; even then it is possible that the anterior ethmoid nerves of the contralateral trigeminal nerve, or perhaps some connection from the isolated ophthalmic neurons by axon reflex, might have carried impulses sufficient to reestablish the mechanism of the referred pain.

CASE 6.—*Migraine relieved by rhizotomy.* (Reference to this case has previously appeared.[25])

Fig. 13 (case 6).—After operation there was complete analgesia in the distribution of the first division and partial loss of pain sensation in that of the second division on the right side.

G. M., a woman aged 38, came to one of us (W. P.) in 1929, complaining of headaches on the right side. There was a family history of migraine. Her attacks of pain had begun at 8 years of age and had come to have a periodicity of about twelve days. She had been free from them only when pregnant. The pain was in the right frontal region, radiating to the right shoulder, and was unbearable even with large doses of morphine. The attacks were preceded by a sense of fatigue, facial pallor and a sensation of fulness in the nose. During the attacks the right eye watered.

Injections in the sphenopalatine ganglion by Dr. W. J. McNally gave only partial and temporary relief. Cervical and upper thoracic sympathetic ganglionectomy and perivascular sympathectomy of the carotid and vertebral arteries on the right side had two results: First, it took away the spread of the head pain to the neck and shoulder; second, it produced for about six months neuritic pain in the right arm and pain in the parotid region on eating. However, the headache continued.

25. Penfield, W.: Operative Treatment of Migraine and Observations on the Mechanism of Vascular Pain, Tr. Am. Acad. Ophth. **37**:50-64, 1932.

In December 1929 a renewed attempt was made to cure the condition. Procaine hydrochloride was injected into the gasserian ganglion during an attack of headache. The needle was inserted into the third division at the foramen ovale. The lower lip and tongue therefore became numb first, but there was no effect on the headache. Next, the upper lip and nose likewise became numb, with no alteration in the headache. As the area of distribution of the ophthalmic division became numb the patient remarked suddenly: "I have nothing to feel the pain with," and her headache vanished. It returned only when the analgesia had worn off.

Consequently, subtotal posterior trigeminal rhizotomy was carried out, the procedure of Frazier being reversed so as to sever the roots of the ophthalmic division. There resulted complete analgesia in the distribution of the first division and partial loss of pain sensation in that of the second, as indicated in figure 13.

In the ten years that have elapsed since this operation there has been no recurrence of headache. For a time she periodically had the feeling that she should be having a headache, but felt no pain. Before operation she had been driven to thoughts of suicide because of her suffering, but she has since become "about the healthiest person you ever saw," to quote from an enthusiastic letter.

This was a case of severe, but typical, unilateral migraine. We assume that the pain in the right frontal region, which originally radiated into the right side of the neck and right shoulder was pain of the referred type, from the right superior sagittal and transverse sinuses. In unilateral migraine there is apt to be a change in the circulatory state of the ipsilateral hemisphere, associated at times with alteration in the function of that hemisphere, especially of the occipital lobe. The nature of these changes will not be discussed at present.

We believe that the pain in this case may have arisen from altered tension on the dural sinuses and that it was relieved by denervation of the sinuses. That the relief of pain was not due to denervation of the cerebral arteries is suggested by the fact that our dissections, at least, have not shown trigeminal fibers to the cerebral arteries. If there are any fibers from the fifth nerve to these arteries, they must be small indeed; moreover, arterial pressure within the large arteries of the two hemispheres must be nearly the same and should give rise to bilateral, not unilateral, pain. That the relief is not due to denervation of the dural arteries is indicated by the fact that middle meningeal arteries are usually supplied by the second and third divisions. However, it should be pointed out, in all fairness, that we have had an unverified suspicion that the meningeal branches may find their way into the posterior root with the fibers of the first division, although peripherally they form part of the second and third divisions (see section on "Dural Nerves in Man"). If the pain in this case had arisen in the meningeal vessels, injection of procaine hydrochloride should have abolished the headache when the second and third branches were anesthetized, but this was not the case.

CASE 7.—*Post-traumatic headache relieved by trigeminal rhizotomy.*

F. G., a milkman aged 53, tripped on a doorstep when delivering milk and fell, striking the right side of his head. There was no loss of consciousness, but he was unsteady on his feet; objects seemed to rotate around him, and for about an hour after he felt dazed. There was no bleeding from the nose or ears and no vomiting. Several hours after the injury he noted a throbbing pain in the right temporoparietal region. Headache had persisted in this region since the accident in June 1935, together with indefinite dizziness.

When he was examined a month after the injury there were tenderness in the right temporal region, slight nystagmus on looking to the left and some unsteadiness of gait. General medical findings were normal; the blood pressure was 100 systolic and 70 diastolic, and routine laboratory examinations gave normal results. A pneumoencephalogram at this time showed no abnormality.

A month later the patient was readmitted to the hospital, and lumbar insufflation of air was carried out, with the patient in such a position that air would enter the subdural space. As the headache persisted after this procedure, right parietal trepanation was done later and the subdural space filled with air directly. This method of treating post-traumatic headache has been discussed elsewhere.[26] At operation an instrument was passed posteriorly and laterally from the burr hole over the occipital lobe, producing pain which resembled the patient's headache. This was repeated twice, with the same result. There seemed to be adhesions between the dura and the arachnoid in this region, as judged by the resistance to the curved instrument. Postoperative roentgenograms showed apparently complete opening of the subdural space. This was followed by complete relief from headache and dizziness; however, the patient returned in six months complaining of a "heavy feeling" over the vertex, and later the headaches reappeared in the right posterior parietal region, several times a week. There was also a constant sensation of "platelike" pressure over the right parieto-occipital region. There was occasional dizziness on stooping.

It was thought that the headache was of a localized meningeal type, which subdural insufflation had failed to cure. Other possible causes of the headache were excluded. There was no compensation factor, and we were convinced that the complaint was genuine. Trial injections of nupercaine into the right trigeminal nerve (third division) were carried out during two attacks of headache. On the first occasion complete block of the third division gave only partial relief, but on the second the same degree of block seemed to give complete relief from the headache. As the anesthesia wore off the pressure sensations returned to the head.

In view of past experiences it was thought advisable to section fibers of the first and second divisions in the posterior root, rather than fibers of the third division. In May 1938, right subtemporal craniotomy was done; the middle meningeal artery was tied, and the mesial two thirds of the posterior root was cut close to the ganglion. The greater superficial petrosal nerve was fully exposed and left intact. Postoperatively, there were complete analgesia over the area supplied by the first division and absence of the right corneal reflex, almost complete analgesia of the cutaneous area supplied by the second division and slight impairment of sensation in the distribution of the third division. This has remained unchanged. There has been no headache in more than a year since operation; however, two unfortunate complications of the operation have prevented the patient

26. Penfield, W., and Norcross, N.: Subdural Traction and Post-Traumatic Headache: Study of Pathology and Therapeusis, Arch. Neurol. & Psychiat. **36:** 75-95 (July) 1936.

from returning to work—mild keratitis in the right eye, which is now healed, and chronic ulceration of the right nasal orifice, which is still under treatment.

In this case, we believe that post-traumatic meningeal headache, which did not respond to other forms of treatment, has been permanently relieved through denervation of the dura mater on the affected side, denervation being effected by section of the mesial portion of the posterior root of the trigeminal nerve.

GENERAL COMMENT AND SUMMARY

It has often been suggested that headaches are due to irritation of the dura and its septums, particularly the area about branches of the meningeal arteries; obviously, however, not all headaches are produced by the same structural mechanism or subserved by the same nerve pathways. Other sources of headache which have been suggested are the cerebral arteries [27] and the walls of the third and lateral ventricles of the brain.[28] Experimental observations on headache will no doubt eventually elucidate the role played by each of these structures.[29]

Most headaches seem to us to be dural in origin, but under the definition of "dural" must be included the dural sinuses and the veins tributary to the sinuses in their course across the subarachnoid space from the brain. It is true that the largest cerebral arteries, i. e., those composing the circle of Willis, seem to be sensitive on palpation, but it is often difficult to be certain that this sensitivity is not due to the attachment of the arteries to the leptomeninges and dura. The arteries within the brain tissue itself are quite insensitive to ordinary mechanical stimulation, although it is possible that there are other more adequate methods of producing pain, such as distention of the walls of vessels.

We have as yet found no fibers passing from the trigeminal nerve to the cerebral arteries. There is, however, the branch from the nervus intermedius of the facial nerve (Chorobski and Penfield [11]) which reaches the middle cerebral artery through the greater superficial petrosal nerve. The efferent fibers of this nerve are parasympathetic and serve as vasodilators for the cerebral vessels, but there are some afferent fibers the ganglion cells of which are situated in the geniculate ganglion. If the largest cerebral arteries are truly sensitive to pain, we suggest that the greater superficial petrosal nerve may carry the sensory fibers in question. Other possible pathways have been reviewed elsewhere.[2]

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27. Fay, T.: The Mechanism of Headache, Tr. Am. Neurol. A. **62**:74-77, 1936. Northfield.[10]

28. Elsberg, C. A.: The Intracranial Pressure in Health and Disease, A. Research Nerv. & Ment. Dis., Proc. **8**:3-6, 1929.

29. Pickering, G. W.: Experimental Observations on Headache, Brit. M. J. **1**:907-912, 1939.

The brain itself is ordinarily quite insensitive. The walls of the lateral ventricles may be compressed or stimulated without sensation in the conscious patient. If, however, the brain is retracted from the falx or the base of the skull, severe pain may result because of traction on one of the veins or granulations which anchor the brain to the dura and its sinuses.

It must be admitted that occasionally electrical stimulation of the brain itself, usually in the temporal region or in the parietal lobe near the superior sagittal sinus, gives rise to pain which may be elicited over a considerable area of the cortex. This rare cerebral pain has invariably the same reference as pain from the nearby dura, and we have been in the habit of explaining it on the theory of escape of current, although the distance of spread sometimes seems too far. Furthermore, meningocerebral scars are occasionally sensitive even after the dura is cut away. It is impossible, therefore, to rule out cerebral pain under certain abnormal conditions.

Dural headaches do arise in the posterior fossa, but this will form the subject of a later communication. The nerve supply of the dura and sinuses of the posterior fossa are described here as arising chiefly in the vagus nerve, with addition of fibers of some sort from the hypoglossal, and possibly from the glossopharyngeal, nerve. Discussion for the present is confined to the dura anterior to the tentorium, including the upper surface of the tentorium and the tentorial sinuses. In cases 1 and 2 it was demonstrated that, at least as far as the 2 patients here were concerned, the areas of dura just described were exclusively innervated by the ipsilateral fifth cranial nerve.

The cranial dura gives rise only to a sensation of pain, whether the stimulus is pressure, traction, heat or electric current. The pain is of two kinds: local and referred.

1. *Local Pain.*—Most of the dural convexity is insensitive, but there are sensitive points in it, and they give rise to pain localized by the patient near the point stimulated. By the convexity is meant all the dura except the falx, tentorium and dural sinuses. The sensitive points are found to coincide with the meningeal arteries, except in the middle and posterior fossae, where nerves pass across the dura on their way to the vascular channels (figs. 1 and 5). The convexity of the dura above the tentorium receives its nerve supply from peripheral branches of the third division of the fifth nerve, and usually also from the second division, with a less constant contribution from the first, either directly or through its tentorial branches.

In certain specimens of dura from Macacus the ganglion cells for these dural nerves seem to have been located on the ophthalmic side of the ganglion, and we suggest the possibility that the branches from

the second and third divisions may have their posterior roots on the ophthalmic side in man, as well as in the monkey.

2. *Referred Pain.*—The ache which results from stimulation of the dural sinuses is usually referred to a distance from the point of stimulation. The direction of this reference is indicated in figure 9. The right lateral wall of the superior sagittal (longitudinal) and the straight sinus and the upper wall of the right transverse sinus are innervated by the ophthalmic division of the right trigeminal nerve, and these walls are easily stretched either by pressure or by traction exerted directly on the sinus. The walls of these sinuses may also be stretched indirectly by pressure on the right side of the falx and tentorium (fig. 10).

An excellent example of true dural pain is case 5, in which atypical neuralgia was due to a cicatrix within the falx (fig. 12) which pulled on the sagittal sinus and thus produced pain referred to the left side of the face and neck. Why did it not produce bilateral pain? Such traction might be expected to affect equally both walls of the sinus. It must have been due to some variation of structure or nerve supply, for when the superior wall of the sinus was stimulated electrically before the dura was opened the pain was referred also to the left, and the same was true when the whole falx and sinus were cut across.

Relief of headache by section of the trigeminal nerve has been a frequent incidental finding in the experience of others (Cushing,[30] Davies [31] and Love and Adson [32]). Cushing, however, pointed out an interesting fact that if the ophthalmic fibers were spared at operation and the others cut postoperative headache occurred on both sides of the head, whereas after complete section of the fifth nerve on one side the ordinary postoperative headache was only contralateral. Harris [33] has produced relief in cases of atypical migraine, which he named migrainous neuralgia, by injection of alcohol into the inner two thirds of the trigeminal ganglion. In these cases there was permanent loss of sensation in the cutaneous areas supplied by the first and second divisions. Such observations suggest that it is the fibers belonging to the first division of the trigeminal nerve which are particularly concerned with the mediation of pain in the head. Smyth [34] has recently recorded a similar observa-

30. Cushing, H.: The Sensory Distribution of the Fifth Cranial Nerve, Bull. Johns Hopkins Hosp. **15**:213-232, 1904.

31. Davies, H. M.: The Functions of the Trigeminal Nerve, Brain **30**:219-276, 1907.

32. Love, J. G., and Adson, A. W.: Effect of Cervicothoracic Sympathectomy on Headache, Arch. Neurol. & Psychiat. **35**:1203-1207 (June) 1936.

33. Harris, W.: The Facial Neuralgias, London, Oxford University Press, 1937, pp. 70-75.

34. Smyth, G. E.: The Systemization and Central Connections of the Spinal Tract and Nucleus of the Trigeminal Nerve, Brain **62**:41-87, 1939.

tion in a case in which the spinal tract of the trigeminal nerve was divided on the right side according to Sjöqvist's method. After the tractotomy there was analgesia over the first and second divisions of the right trigeminal nerve. He said:

> It is interesting to note that headache, which lasted for about a week after the operation, was strictly confined to the left half of the scalp. This fact was spontaneously remarked on by the patient.

In other reports on trigeminal tractotomy the localization of postoperative headache has not been mentioned. We have frequently found, in studying the effect of nupercaine block on chronic unilateral headache, that relief depended on complete block of the ophthalmic portion of the trigeminal ganglion, similar to that recorded in case 6. We have also observed several times that the headache produced by the lumbar injection of oxygen can be prevented on one side of the head by a previous injection of nupercaine in the corresponding trigeminal ganglion; however, there must be loss of the corneal reflex and also loss of pain sensation over the area of skin supplied by the first division or the headache remains bilateral. All these findings point to the importance of the fibers of the ophthalmic division as nerves mediating pain in the head.

All headaches, however, are not relieved by operation on the fifth nerve, as has also been previously pointed out.[35] The observations in cases 1 and 2 reported here bear out this observation.

In case 6 the migraine, which was of classic unilateral type, vanished permanently after subtotal rhizotomy of the ophthalmic fibers. The reason for this is that the dural sinuses were thus denervated on that side of the head. It seems likely that the change in circulation involving the hemisphere on the side of the pain caused the walls of the sinuses to be stretched during each attack of migraine. Such radical neurectomies, however, should always be preceded by differential procainization of the various branches of the fifth nerve.

In case 7 a localized headache of traumatic origin was permanently relieved by subtotal trigeminal rhizotomy similar in type to that performed in case 6. Here it is believed that the affected area of the parietal dura was rendered insensitive through section of the ophthalmic division of the posterior root fibers, even though many of the nerves may have reached the dura by way of the third division. It was pointed

35. Carmichael, E. A., and Woollard, H. H.: Some Observations on the Fifth and Seventh Cranial Nerves, Brain **56**:109-125, 1933. Elsberg, C. A., and Southerland, R. W.: The Etiology of Headache: I. Headache Produced by the Injection of Air for Encephalography, Bull. Neurol. Inst. New York **3**:519-543, 1934. Craig, W. M.: Typical and Atypical Neuralgia of Face and Neck, Proc. Staff Meet., Mayo Clin. **11**:677-681, 1936. Riley, H. A.: Migraine in Children and the Mechanism of the Attack, Bull. Neurol. Inst. New York **6**:387-402, 1937.

out also that some, if not all, of the dural nerve fibers which course across the third division of the fifth nerve probably connect with the first division of the posterior root.

It has been objected that the insensitivity of the dura in cases 1 and 2 and the relief of headache following operation in cases 6 and 7 do not rule out the possibility that sympathetic fibers in the middle meningeal plexus may mediate pain in the head. It is true that in all 4 cases the middle meningeal artery had been ligated during the operative approach to the trigeminal nerve, thus removing most of the sympathetic supply to the dural vessels. These ligations were at much earlier periods, and regeneration of the peripheral sympathetic nerves might have been expected. A more ideal case to test this objection would be one in which the trigeminal root had been sectioned in the posterior fossa. However, in case 3, in which the sympathetic fibers were probably unaffected by the nupercaine, the dura was insensitive only as long as the first division of the ganglion was blocked. Dural pain could be elicited while the second and third divisions were still completely blocked. In case 4 the dura was sensitive though the middle meningeal artery had probably been ligated before at the subtotal posterior root section. Such observations should dispose of this objection. It might also be added that there is no good anatomic evidence for the presence of afferent fibers in the cervical portion of the sympathetic trunk.

In reporting these cases we do not advocate the treatment of all severe unilateral headaches, belonging to the migraine and post-traumatic types, by such a radical means as section of trigeminal roots, but we describe this as one of the methods of radical attack.

In every case in which headache or pain in the head has become truly intolerable the individual pain mechanism should be studied. Radical treatment should then be directed toward removal of the cause or toward interruption of the nerves involved; however, knowledge of the patterns of pain reference and the details of nerve supply to the dura is prerequisite to discriminating radical therapy.

BILATERAL ACOUSTIC NEUROFIBROMAS

FURTHER CLINICAL AND PATHOLOGIC DATA ON HEREDITARY DEAFNESS AND RECKLINGHAUSEN'S DISEASE

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In 1930, Gardner and Frazier [1] reported a family in which von Recklinghausen's disease, in the form of bilateral tumors of the acoustic nerve, had been transmitted as a dominant mendelian trait through five generations. At the time of the original report, 38 of the 217 members of the family were affected. Necropsy was performed on 2 members of the family and revealed bilateral acoustic neurofibromas. After the publication of the first report, symptoms of a tumor of the spinal cord developed in 1 of the affected members. This tumor was removed and likewise proved to be a neurofibroma; the case was subsequently reported by Gardner.[2]

The present report, the third concerning this family, deals chiefly with the pathologic material obtained from 4 members since the last publication.[3] One of these members (case 4) represents the only case thus far observed in which the disease has been recognized in the sixth generation.

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1. Gardner, W. J., and Frazier, C. H.: Bilateral Acoustic Neurofibromas: A Clinical Study and Field Survey of a Family of Five Generations with Bilateral Deafness in Thirty-Eight Members, Arch. Neurol. & Psychiat. **23**:266-300 (Feb.) 1930; Hereditary Deafness Due to Bilateral Acoustic Tumors: Clinical Study and Field Survey of a Family of Five Generations with a History of Bilateral Deafness in Thirty-Eight Members, Ann. Otol., Rhin. & Laryng. **39**:974-986 (Dec.) 1930.

2. Gardner, W. J.: Tumor of the Spinal Cord Associated with Bilateral Acoustic Tumors: Report of a Case, Arch. Neurol. & Psychiat. **24**:1014-1022 (Nov.) 1930.

3. The histologic sections were stained with hematoxylin and eosin and phosphotungstic acid hematoxylin and by Perdrau's silver impregnation method for connective tissue, Fincher's silver technic, Cajal's and Bielschowsky's silver methods for nerve fibers and, in some instances, by various stains for myelin sheaths. Some of the preparations, particularly those of necropsy material, suffered from the fact that the tissue was obtained long after death. However, in no instance were the postmortem changes so great as to interfere with a relatively detailed study of the tissue or to prevent recognition of the tumor type.

The family tree, brought up to date, is included in this report, and with it a short résumé of the essential data on each of the affected members. The symbols and general scheme of the chart have not been changed, so that reference may be made to the original article (fig. 1). It is assumed that all members of this family who were deaf, or deaf and blind, had bilateral acoustic tumors. This assumption has proved correct in the 6 members on whom operation or necropsy was performed. These 6 members are represented on the chart as *IVB3a, VA3, VA6, VA7, VA9* and *VJ*. In addition, it is assumed that the members with absence of vestibular reactions without deafness had the disease in an early stage. This has proved true in the case of *IVG7* and *VA9*, who in 1929 had absence of vestibular reactions without deafness and who subsequently presented the complete picture of bilateral acoustic tumors. Therefore, it may be said that loss of the vestibular reactions constitutes the earliest sign of these tumors.

THE FAMILY TREE

A short résumé of the important clinical and pathologic data on the affected members of the family follows. More detailed information concerning many of these persons, as well as the unaffected members, may be found in the original report by Gardner and Frazier.[1]

The only information available concerning *Z*, the earliest known progenitor of this family, is that he was completely deaf. His son *A* was totally deaf for some time prior to his death (from cancer of the face), at the age of 72. The 11 siblings of A moved west with their father about 1850, and have not been traced. It was said that "several, if not all," of them subsequently became deaf. *A* married twice and had 4 children by each wife. A study of the issue of these two marriages indicates that the disease is transmitted as a dominant mendelian trait; that is, it is transmitted only by the affected members to approximately half their offspring. In some cases it appears that less than half the offspring are affected. This apparent discrepancy is due to the fact that some of the members died before they were old enough for symptoms of the disorder to develop.

III, a woman, became deaf before she died, at the age of 90. The age at the onset of deafness is not known. She was married but bore no children.

IV, a woman, became deaf but died of a cause other than the tumor at the age of 48. The exact age at the onset of deafness is not known.

V, a woman, was deaf for many years and died at the age of 85. The exact age at the onset of deafness is not known.

VI, a man, had slowly progressive deafness before his death at the age of 49. For one year prior to his death he suffered from severe headaches and was totally blind.

VII, a man, was completely deaf for five or six years and blind for one year prior to his death, at the age of 49. He suffered from moderately severe headaches.

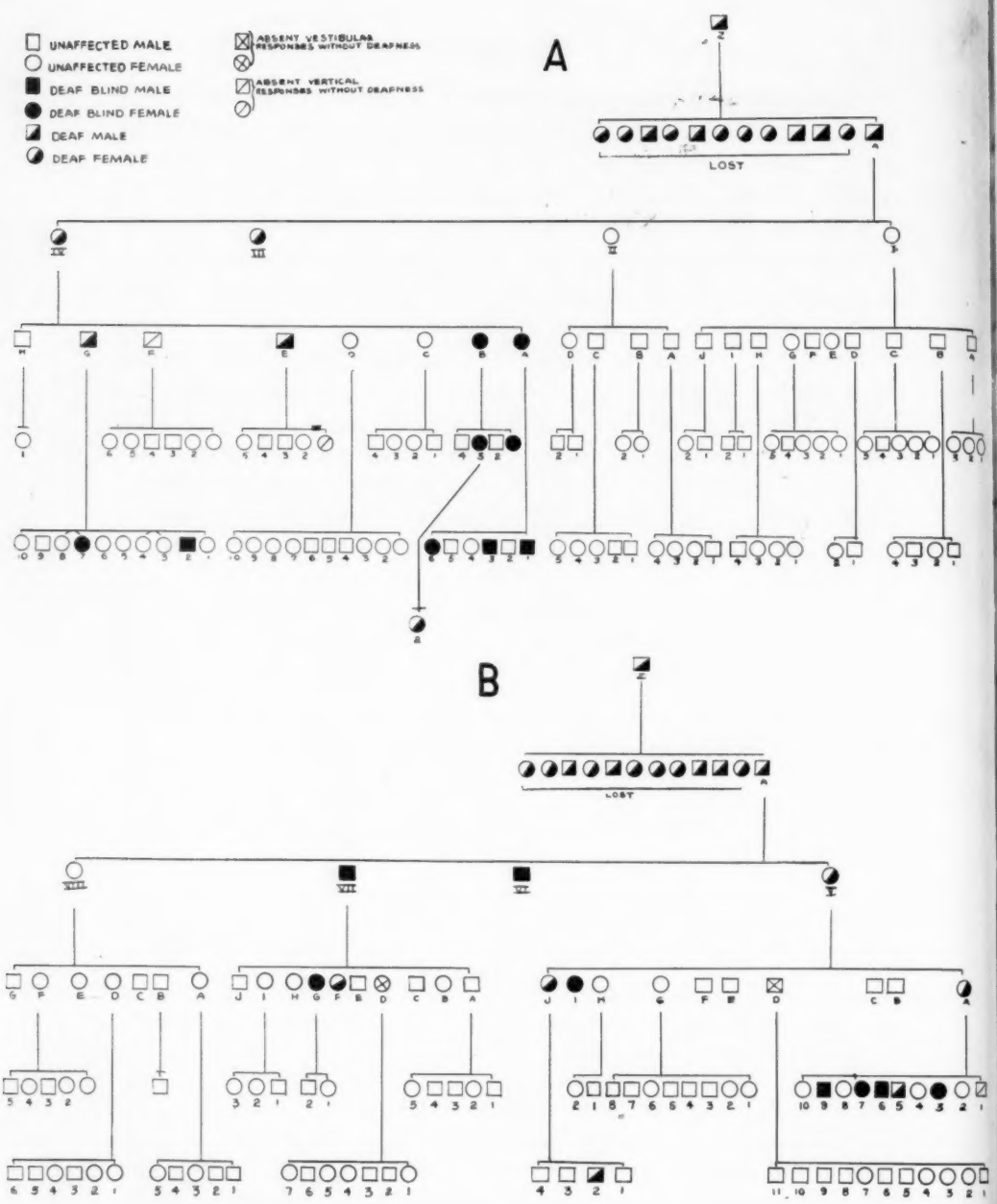

Fig. 1.—*A*, issue of the first marriage of *A*; *B*, issue of the second marriage of *A*. The first generation is represented by *Z*; the second by *A*; the third by Roman numerals; the fourth by capital letters; the fifth by figures, and the sixth by small letters. To conserve space, symbols for the numerous members of the fifth generation have been placed in two rows. The ages may be determined by reference to the text or to the original publication.[1]

IVA, a woman, died at the age of 46, after having been totally deaf for from five to six years and blind for one year.

IVA1, a man, became totally deaf at 23 and blind at 24 years of age and died at the age of 26.

IVA3, a man, became blind at 32 and died at 37 years of age. He was deaf, but the age of onset is not known.

IVA6, a girl, became deaf at 16 and blind at 20 years of age. She died at the age of 21.

IVB, a woman, died at the age of 35. She was said to have been blind for one year prior to her death and deaf for many years.

IVB1, a woman, had been deaf for from two to three years and blind for one year prior to her death, at the age of 26.

IVB3, a woman, was deaf for two to three years and blind for one year prior to her death, at the age of 26. She was the mother of 1 child, who was 15 years old at the time of the original report, in 1930. This child (*IVB3a*) is one of the subjects of the present report.

IVB3a, a woman aged 24, is one of the subjects (case 4) of the present report.

IVE, a man aged 41 at the time of the first report, in 1930, had at that time had increasing deafness in the left ear for six years and had been completely deaf in the right ear since the age of 18. There was a history of occasional tinnitus in the left ear for twelve years. Examination revealed slight hearing in the left ear and total deafness in the right. A dense cataract was present in the left eye. There were sluggish corneal reflexes bilaterally and total absence of vestibular responses. The clinical diagnosis was bilateral acoustic tumors. The patient subsequently died in an accident, and permission for necropsy was not obtained.

IVE1, a girl aged 10 years, complained of bilateral tinnitus of more than a year's duration. Rotation tests gave subnormal responses from the horizontal canals; douching the ears elicited no responses from the vertical canals. There was no deafness.

IVF, a man aged 44, had no history of tinnitus or deafness. Examination revealed absence of responses from both vertical canals and sluggish responses from the horizontal canals on douching the ears with cold water.

IVG, a man aged 61, with a history of total deafness for over twenty years, had bilateral tinnitus associated with occasional attacks of headache and vertigo. Examination disclosed moderate hypalgesia in the distribution of the left fifth cranial nerve and a sluggish left corneal reflex. There was no blindness and no cerebellar signs. Vestibular responses were absent both on turning and on douching with cold water. The clinical diagnosis was bilateral acoustic tumors.

IVG2, a man, had a history of bilateral tinnitus beginning at the age of 26 and gradually progressing to deafness, which at the age of 31 was complete on the left side and almost complete on the right. He complained of dizziness, weakness and inability to walk in the dark. There was also diplopia. On examination the gait was ataxic; the Romberg sign was positive, and there was marked incoordination in the finger to nose test. Speech was scanning, and there was bilateral papilledema. Roentgen examination disclosed erosion of the posterior clinoid processes. He was completely blind and deaf prior to his death, which occurred at the age of 34. The clinical diagnosis was bilateral acoustic tumors. Permission for necropsy was not obtained.

IVG7, a woman, one of nonidentical twins, was 22 when examined in 1929. There was a history of unsteadiness, with difficulty in walking after dark, for five years. Examination revealed a slightly positive Romberg sign, questionable hypalgesia in the distribution of the left fifth cranial nerve and a sluggish left corneal reflex. The patient was unable to walk in the heel to toe test. There was no response from the horizontal canals on turning and no response from the right ear on douching. Examination could not be concluded because of apprehension on the part of the patient. The clinical diagnosis at that time was probable early bilateral acoustic tumors. A subsequent report indicates that this patient became totally deaf and blind during the fall of 1932 and that the staggering became more severe. She died a few months after the onset of deafness and blindness, and repeated attempts to obtain permission for necropsy were of no avail. The subsequent course in this case confirmed the earlier diagnosis of bilateral acoustic tumors.

VA, a woman who was completely deaf for many years, was said to have died of a stroke at the age of 50.

VA1, a man aged 38, with a history of occasional tinnitus presented sluggish corneal reflexes bilaterally. Douching gave no response from the vertical canals on either side and a poor response from the horizontal canals.

VA3, a woman aged 34, was totally deaf and blind. She is one of the subjects of the present report (case 1).

VA5, a man aged 30, when examined in 1929, had complete deafness in the right ear, which was first noticed at the age of 14, and slowly progressing deafness in the left ear, which had been present since the age of 16. There were episodes of complete deafness lasting from three to seven days for the past ten years. Tinnitus had been present since the age of 15. He suffered from occasional headaches, which were relieved by catharsis. Examination disclosed hearing loss of 93.5 per cent on the right and of 57.2 per cent on the left. There was slight impairment of the right corneal reflex. Bárány examination disclosed entire absence of the vestibular response, with the exception of a minimal reaction from the left horizontal canal. Roentgen examination revealed a deformity of the inner portion of the right petrous bone, and possibly of the left. The clinical diagnosis was bilateral acoustic tumors. This man is now almost totally deaf, but presents no evidence of increased intracranial pressure.

VA6, a man aged 28, was found to have bilateral acoustic tumors at necropsy. The results of complete clinical examination and necropsy were reported in detail in the original communication by Gardner and Frazier.

VA7, a woman aged 26 when she died, had been blind for about six months and deaf for six years prior to her death. On examination she was stuporous, unable to speak and totally blind. There were chronic conjunctivitis, corneal ulceration and evidence of subsiding optic neuritis. Necropsy revealed bilateral acoustic tumors. This case was also reported in detail in the original communication by Gardner and Frazier.

VA9, a man aged 21, is one of the subjects of the present report (case 2).

VA10, a woman, has bilateral deafness and cutaneous nodules according to a report recently received from Dr. L. W. Davison, of Danville, Pa. There are early papilledema and absence of the vestibular responses. This information arrived too late to be included in the genealogic chart (fig. 1).

VD, a man aged 56, had a history of no significance. Examination revealed bilaterally diminished corneal reflexes, most marked on the right. Hearing was normal, but the vestibular responses were totally absent on douching the ears with cold water.

VI, a woman, was known to be both deaf and blind at the time of death. Further information was lacking.

VJ, a woman aged 56, is one of the subjects of the present report (case 3).

VJ2, a man aged 37, was almost completely deaf when examined in 1929. Tinnitus was first noticed in the right ear at the age of 16 and in the left ear about two years later. Deafness began after the onset of tinnitus, and at the time of examination it was complete on the right and almost complete on the left. The patient had slight left external strabismus and bilaterally sluggish corneal reflexes. There were no responses from the vestibular apparatus, either on turning or on douching, with the exception of a questionable response from the left horizontal canal. Roentgen examination of the skull revealed a suggestion of erosion of the right petrous bone on the inner portion of its posterior surface. The clinical diagnosis was bilateral acoustic tumors. There has been no recent examination in this case, but the patient is said to be in good health.

VIID, a woman aged 55, had a history of occasional tinnitus. The corneal reflexes were absent bilaterally. Hearing was normal. No vestibular responses could be obtained from either side on caloric stimulation.

VIIF, a woman aged 32 at the time of death, had been paralyzed on one side of the body and had been totally deaf for several years prior to her death.

VIIG, a woman, had been deaf for three years and blind for one year prior to her death, at the age of 32.

REPORT OF CASES

CASE 1.—*Total deafness for nineteen years; blindness for twelve years. Necropsy six weeks after death. Bilateral acoustic neurofibromas, with a small meningioma adherent to one of these growths.*

VA3, a woman aged 40 when she died in 1935, had been completely deaf since the age of 21. It was believed that the onset of deafness was gradual and associated with tinnitus. Aside from the deafness, she was well until the age of 28. At that time, after the birth of a child, she suffered from headaches, vomiting and rapid failure of vision.

When examined in 1923 she was totally deaf and blind. There were choking of the optic disks of 3 D. and marked paralysis of the right facial nerve of the peripheral type. Gait was ataxic. Vestibular tests gave no response, except possibly from the left horizontal canal. The spinal fluid pressure was 32 mm. of mercury.

The patient was examined again in 1929, at which time she could walk only with support. There were severe ataxia of the arms and legs and marked spontaneous nystagmus. Both corneas were anesthetic, and the right facial nerve was completely paralyzed. There was complete optic atrophy. Because of her blindness and deafness, the relatives had learned to communicate with her by spelling out the words on her right palm, using her left index finger to draw the letters. Speech was loud, monotonous and dysarthric. The patient became progressively more helpless, and died on July 25, 1935. On Sept. 3, 1935, permission was obtained for disinterment of the body and postmortem examination of the brain.

Pathologic Observations.—The body was poorly preserved, and this was especially true of the cerebrum, which was the site of enormous hydrocephalus, involving the lateral and the third ventricles. The only tumors were those which occupied the cerebellopontile angles (fig. 2). The spinal cord was not examined.

The growth on the right side measured approximately 6.5 by 7.5 cm. in diameter and was light grayish yellow. The external surface was nodular, especially the medial aspect, which had been in contact with the brain stem and cerebellum. The tumor was well encapsulated and was easily shelled out of its bed, which consisted

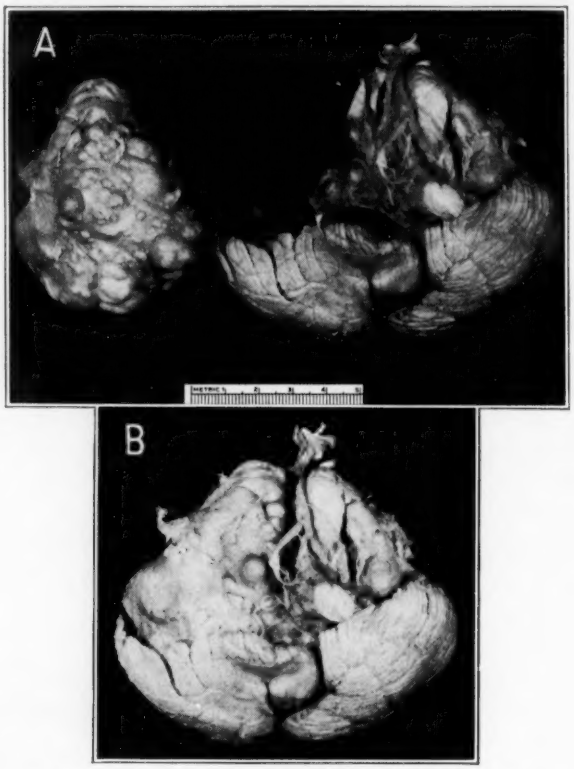

Fig. 2 (case 1, *VA3*).—*A,* brain stem, cerebellum and bilateral acoustic tumors. The fifth nerve can be seen to pass over the superior aspect of the tumor on the right side. *B,* the tumor on the right has been removed from its bed to show the marked nodularity of the growth, unusual for a neurofibroma. The marked compression of the cerebellum and brain stem is evident.

of the superior and inner aspects of the right lobe of the cerebellum and the right side of the pons and medulla. The cranial nerves were easily separated from the tumor, with the exception of the seventh and eighth, which entered the substance of the growth. The fifth cranial nerve could be identified as a thin ribbon of tissue which passed over the superior and anterior aspects of the tumor.

The tumor was enveloped by a closely applied, thin, transparent membrane, which appeared to be the pia-arachnoid. The tumor was firm and was cut with

considerable resistance. Most of the nodules which were apparent on external examination could be identified on the cut surface; several of these showed areas of dark gray discoloration, undoubtedly due to degenerative changes. There was no gross calcification or cyst formation. A small area, about 1.5 by 1 cm. in diameter, at the inner and lower aspect of the tumor was unlike the remainder of

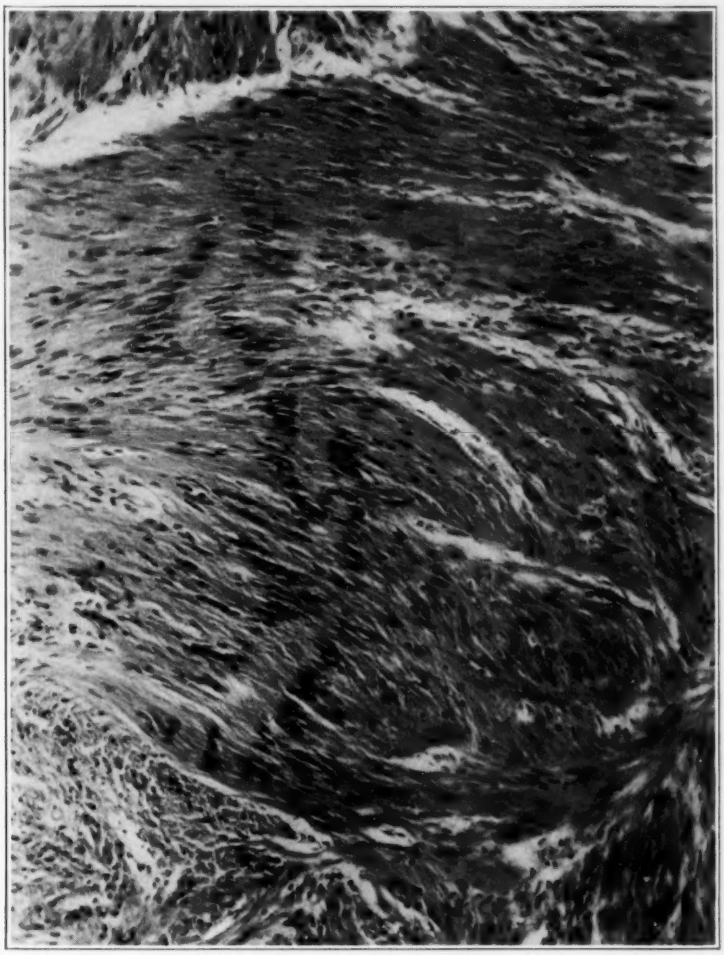

Fig. 3 (case 1, *VA3*).—Section of tissue from the neurofibromatous portion of the tumor on the right. Note the marked streaming of the cell bundles and the characteristic nuclear palisades (see fig. 5.) Hematoxylin and eosin; × about 136.

the tissue. Here the tissue was granular and friable and had a reddish gray color. This area was situated on the surface of the tumor and was poorly defined.

The growth on the left was about half the size of that on the right. Grossly, it was of the same character and differed only in that the external surface was somewhat less nodular and the cut surface showed less definite whorl formation.

It had caused marked indentation of the left lobe of the cerebellum and the left side of the brain stem, but to a lesser degree than on the right. Section of the tumor revealed no area of reddish gray tissue, such as was found on the right.

The right cerebellar lobe was largely destroyed by pressure from the tumor and was reduced in most places to a thin shell of tissue, which measured from 2 to 3 mm. in thickness. The brain stem suffered severely from being wedged between the two tumors. At the pons it measured less than 2 cm. in width, and it was narrowest at the medulla, where it measured slightly less than 1 cm. The entire brain stem was displaced to the left, and the basilar artery, which had maintained its normal position, ran a straight course along the edge of the defect produced by the tumor on the right.

Histologically, the bulk of the tumor on the right was a fairly typical neurofibroma. The picture was complicated, however, by the presence of a second growth, a meningeal tumor which had been represented in the gross specimen by the small, reddish gray area previously referred to.

The microscopic appearance of the neurofibromatous portion of the tumor varied somewhat in different places. In some areas the tissue was composed of interlacing bundles of spindle-shaped cells which had indefinite cell boundaries and elongated, chromophilic nuclei. In such areas there were a number of typical nuclear palisades, but these were not a prominent part of the microscopic picture (fig. 3). The stroma of the tumor consisted of wiry, argentophilic fibers. These lay parallel to one another in bundles which tended to interlace and stream in every direction.

In other areas the tissue was less orderly. There were many foci in which the tissue was reticular and appeared as a tangle of fibroblasts, Schwann cells and collagen fibers. In such a "myxomatous" area, clusters of large, polygonal "foam cells" could be identified, which were apparently fat-laden macrophages.

Owing to the marked streaming in places, there was a suggestion of whorl formation in parts of the tumor. However, there were no definite cell whorls in the neurofibromatous portion of the growth. Unmyelinated nerve fibers could be identified in many of the sections stained by Cajal's method.

Sections through the meningeal tumor disclosed that this growth had arisen in the leptomeninges, which enveloped the larger tumor. Microscopically, this tumor corresponded with that classified by Cushing and Eisenhardt as type II, variant 3.

The tissue was uniform in character and was composed essentially of small, compact cell whorls (fig. 4 *A*). In some areas these were in close approximation without intervening tissue, while in others there were small islands of tumor tissue between the whorls. The stroma consisted of an open network of rather coarse, irregular collagen fibers which ran between the cell whorls. A considerable portion of the tumor was composed of a relatively dense mass of psammoma bodies, which could be seen in various stages of calcification (fig. 4 *B*). In some sections these calcospheres were in close approximation, while in others there was a variable amount of intervening tumor tissue.

Of particular interest was the relation between the meningeal growth and the neurofibroma. The greater portion of the meningeal tumor was spread out over a small area of the surface of the neurofibroma. There was no direct invasion of the larger tumor, but small strands of meningeal tumor could be followed deep into crevices formed by the relatively discrete nodules of the neurofibroma (fig. 5). This was evident in many sections. Special stains failed to reveal the presence of nerve fibers in this tumor, either within the cell whorls or in the tissue between the psammoma bodies.

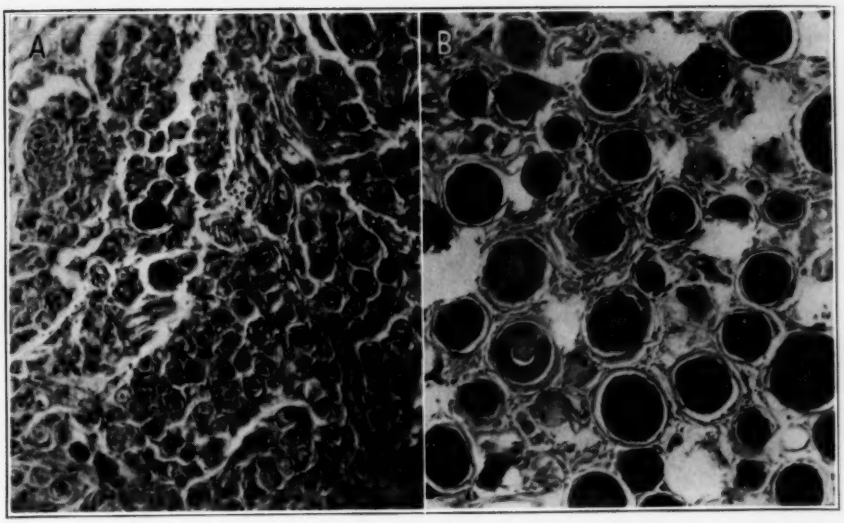

Fig. 4 (case 1, *VA3*).—*A*, section from the cellular portion of the meningeal tumor investing part of the right acoustic tumor. Note the characteristic cell whorls and the occasional psammoma bodies (see fig. 5). *B*, section from the psammomatous portion of the meningeal tumor. Note the intervening tumor tissue (see fig 5). Hematoxylin and eosin; × about 85.

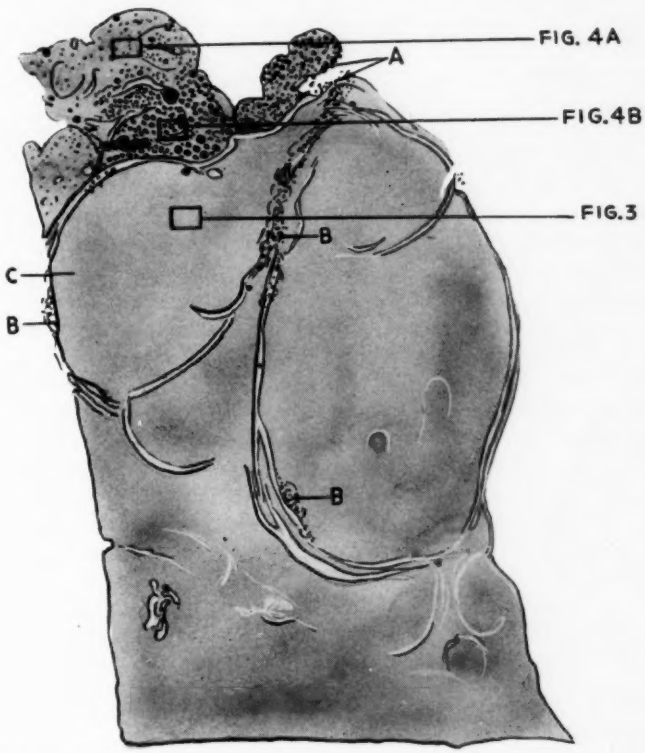

Fig. 5 (case 1, *VA3*).—Drawing from a preparation of the right acoustic tumor in which both growths were present. *A*, leptomeninges infiltrated with meningeal tumor tissue; *B*, meningioma investing the nodules of the neurofibroma (*C*), without actually invading the latter tumor. × 4.

Microscopically, the tumor on the left was similar to that on the right. However, although there was marked streaming of cell bundles; nuclear palisades were less evident, and the tissue in general appeared more like that of the neurofibroma than the perineural fibroblastoma (Penfield). The Perdrau stain disclosed bundles of wiry argentophilic fibers, which interlaced and streamed in all directions. In a few places there was a tangled, disorderly appearance of the tissue. Unmyelinated nerve fibers were present and were relatively easy to find.

The final diagnosis was bilateral acoustic neurofibromas with an associated meningioma on the right.

Meningiomas occur commonly as a part of the picture of central neurofibromatosis, in which case they are frequently located beneath the tentorium. Also, occasional cases have been described in which a small meningeal tumor was observed in the subtentorial region close to a unilateral acoustic tumor.[4] In none of the reported cases, however, was the relation between the two growths similar to that in the case described here.

CASE 2.—*Symptoms of acoustic tumor beginning at the age of 17. Intraspinal neurofibroma removed at the age of 23. Increasing symptoms of acoustic tumors at the age of 26. Removal of left acoustic tumor at the age of 28.*

VA9, a man aged 31, at the time of writing, had always been acutely aware and apprehensive of the disease which had successively attacked his mother, 2 sisters and 2 brothers. Early in our contact with him he attempted to conceal significant symptoms which he greatly feared. After the difficulty became more manifest the following history was obtained.

Beginning at the age of 17, he noticed occasional mild tinnitus and slight unsteadiness on his feet, especially after dark. The tinnitus became more constant at the age of 21, but he was not aware of loss of hearing. At this time, however, audiometer studies revealed mild bilateral nerve deafness. Vestibular tests showed that the semicircular canals were nonfunctioning, with the exception of the left horizontal canal, which gave a considerably diminished response. Shortly after this examination there developed symptoms of a tumor of the spinal cord; i. e., muscular cramps in the left hand, followed by weakness and wasting of this hand, and then weakness of both legs. Constipation and occasional rectal incontinence were also present.

At the age of 23 examination revealed weakness and spasticity of the left hand, with atrophy of the hypothenar eminence and of the interosseus muscles. The grasp of the right hand was slightly weak. Both lower extremities were weak and spastic, and there was impairment of tactile, pain and thermal perception on both sides up to the level of the eighth cervical dermatome. The Romberg sign was strongly positive, and a fine horizontal nystagmus appeared on lateral gaze. Audiometer studies disclosed normal hearing in the right ear and mild nerve deafness in the left. Hearing was better than it had been two years before, but the vestibular responses were about the same. There was complete subarachnoid block on lumbar puncture. At operation an encapsulated tumor was

4. Gardner, W. J., and Turner, O. A.: Multiple Intracranial Tumors: A Discussion of the Relationship of Meningeal to Acoustic Tumors and a Report of a Case, J. A. M. A. **113**:111-113 (July 8) 1939.

seen on the anterior root of the left eighth cervical nerve and was removed.[2] Microscopically, the tumor proved to be a typical neurofibroma. After operation the symptoms of disturbance in the spinal cord rapidly improved.

At the age of 26 the symptoms of tumor of the eighth nerve began to increase. The gait became increasingly uncertain, hearing failed and there developed occasional dull headaches in the right frontal region. At the age of 28 examination showed advanced nerve deafness on the left side, with only slight loss, mostly for high tones, on the right. The semicircular canals did not respond at all to either turning or douching. The optic disks showed 2 D. of choking, and the corneal reflexes were sluggish. Coarse horizontal nystagmus was present on lateral gaze; the Romberg test was mildly positive, and there were mild dysmetria and marked adiadokokinesis. The gait was lumbering, swaying and wide based.

Left suboccipital craniotomy disclosed a large, firm, nodular tumor occupying the left cerebellopontile angle. The ninth, tenth and eleventh cranial nerves could be seen to pass about the inferomesial surface of the tumor to enter the jugular foramen. The fifth, seventh and eighth nerves were not in evidence. Tumor tissue was removed piecemeal until only the anterior portion of the capsule remained. This was left in order to avoid the occurrence of facial palsy. The postoperative course was uneventful; choking of the optic disk subsided, but the patient's symptoms were only slightly improved.

A report in September 1939 indicated that the patient was totally deaf, and dysarthria had progressed so that it was difficult for his relatives to understand what he said. He was scarcely able to walk and had periods of retention of urine and feces, alternating with periods of incontinence. The patient committed suicide Oct. 8, 1939. Permission for necropsy was not obtained.

Pathologic Observation.—The total amount of tissue which reached the laboratory weighed 7 Gm., and the largest piece measured 1.5 cm. in its greatest diameter. The fragments were all similar and consisted of moderately firm, yellowish brown, friable tissue.

On microscopic examination the tumor proved to be a fairly characteristic neurofibroma. The neoplastic cells were spindle shaped, with an abundance of poorly defined cytoplasm and relatively large, elongated and often irregular nuclei (fig. 6). Palisading of nuclei was present, but was not a marked feature of the tumor. The general pattern of the tissue was typical in that there was a linear arrangement of both the nuclei and the cells. The Perdrau stain revealed interlacing bundles of even-calibered, argentophilic fibers. A large part of the tumor was degenerate and had a loose, reticular appearance. In such areas streaming was absent and the nuclei were small, round and wide spaced, while the collagenous fibers were fragmented and not arranged in a definite pattern. Specific stains disclosed occasional nerve fibers within the tumor tissue.

While in this case only one acoustic tumor was removed at operation, there can be no doubt from the clinical findings that a similar lesion existed on the opposite side. In this case the diagnosis stood between uncomplicated bilateral acoustic tumors and diffuse involvement of the central nervous system, i. e., central neurofibromatosis. It is not unlikely that the patient had additional growths involving the central nervous system. It is not improbable, also, that in other affected members of the family there may be or may develop tumors of other portions of the central nervous system.

CASE 3.—*Deafness of thirty-two years' duration, with observation at necropsy of small bilateral acoustic tumors.*

V.J., a woman aged 58 at the time of her death in September 1930, was difficult to interrogate, and her memory was probably faulty. Progressive deafness began at the age of 26, the right ear being affected first. She stated that tinnitus began

Fig. 6 (case 2, *VA9*).—Section from a tumor of the left eighth nerve. Note the interlacing pattern of the cell bundles and the characteristic nuclear palisades. Hematoxylin and eosin; × 125.

at the age of 44, when she had sustained a fracture of the nose in an automobile accident. She also experienced some numbness of the face after this accident. Occasional dizziness and staggering began at the age of 49.

The patient was 56 years of age when she was examined. She presented no nodules of the skin. There was hypalgesia in the distribution of the fifth cranial

nerve on the right side, and the corneal reflex on this side was diminished. She was totally deaf, and there was no response from either vestibular nerve in the turning or douching test. The voice was loud and monontonous but not dysarthric. The Romberg test was positive and the gait slightly ataxic, but there was no nystagmus. The Wassermann reaction was weakly positive. Roentgenograms of the skull revealed a suggestion of erosion on the inner portion of the posterior surface of the right petrous bone.

This patient died of gangrene of the lower extremities in September 1930. Two months after death, permission was obtained to disinter the body and examine the head.

Pathologic Observations.—The body was fairly well preserved. There were no supratentorial tumors, and the ventricles were of normal size and shape. A good view of the cervical region of the cord was obtained through the foramen magnum; no tumors of the spinal cord were seen. In each cerebellopontile angle was a small tumor, which had arisen from the corresponding eighth nerve (fig. 7).

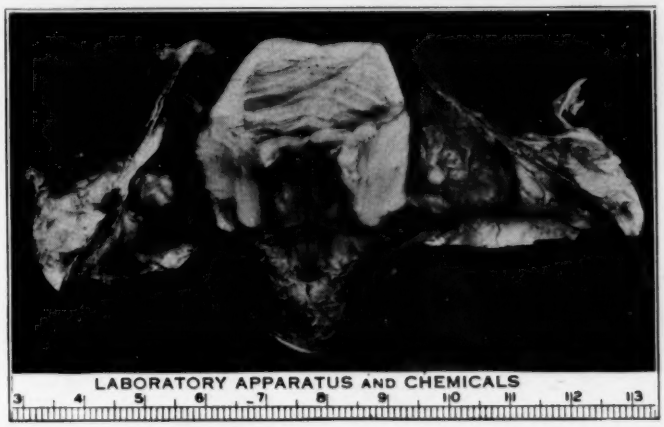

Fig. 7 (case 3, *VJ*).—Gross appearance of the bilateral tumors of the acoustic nerve. Note their small size and their attachment to the internal auditory meatuses.

The tumor on the right was roughly spherical and measured about 1.5 cm. in diameter. The external surface was irregular, rough and light yellow in the formaldehyde-fixed specimen. The cut surface was of the same color, somewhat granular and without gross whorl formation or calcification. The growth was flattened against the porus acusticus, to which it was firmly adherent. The tumor on the left measured about 1 cm. in diameter and had the same gross appearance as that on the right. A block of tissue taken through the entire thickness of the tumor exposed the porus acusticus, which was filled with tumor tissue.

The seventh and eighth nerves on each side could be traced from the pons into the capsule of the tumor. The trigeminal nerves were not involved by the growth, the left being entirely free from the tumor and the right having been displaced slightly by the anterior portion. Both growths were well encapsulated and gave no evidence of invasion. Roentgenograms of the specimen obtained at necropsy disclosed internal auditory meatuses of normal size, but that on the left showed slight irregularity of the margin, not sufficient, however, to be clinically significant.

Microscopic examination of both tumors showed typical neurofibromas. Each had a definite, but thin, capsule composed of moderately dense collagenous tissue. The growth on the right consisted chiefly of compact bundles of spindle cells with poorly defined cytoplasmic boundaries and relatively large elongated nuclei (fig. 8*A*). The latter, for the most part, had a fine chromatin network and often one or more nucleoli, which stained deeply. The cell bundles showed marked streaming and interlacing, and there were occasional large whorl formations. Small nuclear palisades could be seen, but these did not form a prominent part of the picture. A portion of the tissue consisted of a loose tangle of neoplastic cells and collagenous tissue with no streaming or definite pattern formation. These areas were unlike the reticular, edematous foci seen as a result of degenera-

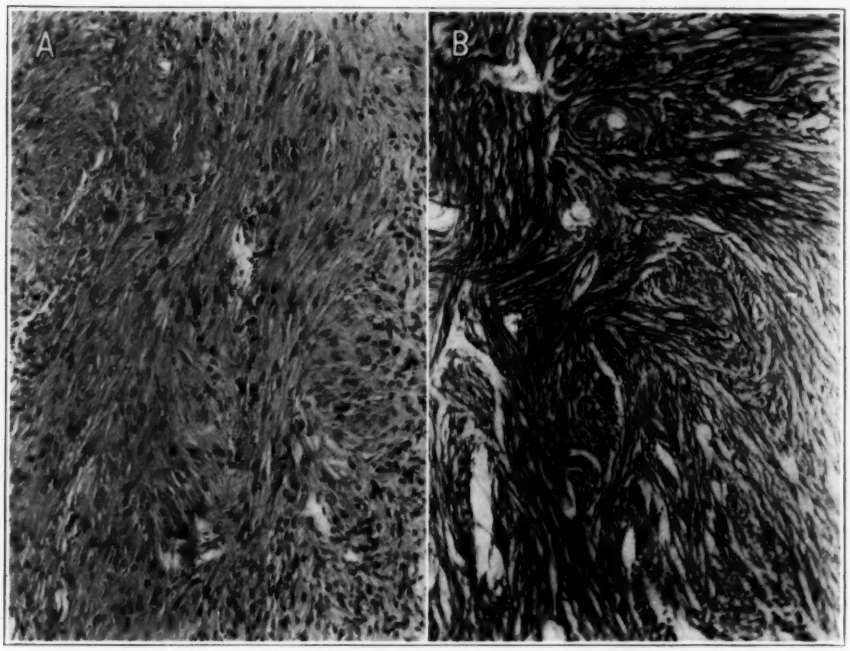

Fig. 8 (case 3, *VJ*).—*A*, section from the tumor of the left acoustic nerve, showing the streaming cell bundles and the typical pattern of the tissue. Hematoxylin and eosin; × about 85. *B*, section of the tumor shown in *A*, illustrating the character of the stroma. Note the wiry, argentophilic fibers, which tend to be arranged parallel with each other in bundles which interlace and stream in all directions. Perdrau connective tissue stain; × about 85.

tion. There were numerous moderate-sized blood vessels scattered throughout the tissue, some with well developed and relatively thick walls and others with but a single layer of endothelium. The Perdrau stain revealed the presence of broad bands of argentophilic fibers, which interlaced and streamed in various directions to form the characteristic pattern so evident in the hematoxylin and eosin preparations (fig. 8*B*). The tumor on the left differed little from that on the right.

Although acoustic tumors of the small size of this tumor have been described by other authors, in no instance have they been bilateral. The history in this case suggests that they had been present in some form for more than thirty years. This fact, correlated with their small size, leads one to agree with Cushing and Eisenhardt [5] that bilateral acoustic tumors tend to a more slowly progressive course than do the solitary growths.

This patient's son has likewise been deaf for thirty years, but is otherwise not inconvenienced by the disease.

CASE 4.—*A member of the sixth generation. Complete deafness, with clinical picture of rapidly growing bilateral acoustic tumors. Removal of right acoustic tumor in 1936.*

IVB3a, a woman aged 24, who was admitted to the Cleveland Clinic Hospital in April 1936, presented the chief complaint of bilateral deafness. About one year before admission the patient noticed tinnitus in both ears, but hearing was normal at that time. Within four months the hearing was poor in the left ear and absent in the right. At the time of admission she was completely deaf in both ears. Frequent headaches began at the same time as the tinnitus. There had been no visual disturbances and no vomiting. She stated that her balance was good and that there was no difficulty in walking in the dark. Close questioning revealed that about six years previously she had, for a short time, been subject to mild transient attacks resembling true aural vertigo.

Examination disclosed a moderately positive Romberg sign, coarse horizontal nystagmus, absence of corneal reflexes and bilateral choked disks of 1 D. There was no anesthesia or weakness of the face. The extraocular muscles were normal. Hearing was entirely absent on the right and practically absent on the left. Bone conduction was absent bilaterally. Suboccipital tenderness was present, but not marked. There was no dysmetria. The tendon reflexes were all active and equal on the two sides. Douching for five minutes gave no response from either vestibular apparatus. Examination revealed no nodules or areas of pigmentation in the skin.

A diagnosis of bilateral acoustic tumors was made and the patient discharged for further observation. She was seen again in June 1936, at which time the headaches had become more frequent and more severe. These were chiefly frontal but occasionally suboccipital. In addition, the dizziness (i. e., whirling sensation) which she had experienced some years before had recurred.

The papilledema previously described had increased slightly. Perimetric examination gave normal results. Roentgen examination of the skull disclosed no erosion of the petrous ridges. The gait had become mildly ataxic.

At this time the patient underwent right suboccipital craniotomy with total removal of an acoustic tumor. The operative procedure was long and difficult. The tumor was large, measuring about 5 cm. in diameter. It was firm, tough and vascular; the contents were curretted with great difficulty. The patient suffered from postoperative paralysis of the fifth, seventh, ninth, tenth and eleventh cranial nerves on the right side and some weakness of the right arm. She was discharged on the fifteenth postoperative day. The palsies of the cranial nerves, with the exception of the seventh, subsequently improved, and a recent report stated that she was in good health.

5. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behavior, Life History, and Surgical End Results, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

Pathologic Observations.—The tissue removed at operation was of the usual light yellow color, but was somewhat firmer and less friable than that in the cases previously described. Microscopically, the tumor was a neurofibroma, which was the seat of moderately severe degenerative changes. The typical interlacing pattern of the tissue was interrupted in many places by areas in which the tissue appeared edematous and reticular (fig. 9 *A*). In many such foci vacuolation of the cytoplasm was pronounced. Cell boundaries were practically absent, and the nuclei appeared small, round and hyperchromatic. In some areas the process was advanced almost to the stage of liquefaction necrosis. Here the tissue was replaced by a pink-staining, homogeneous matrix in which occasional pyknotic nuclei and fine fibrils were present.

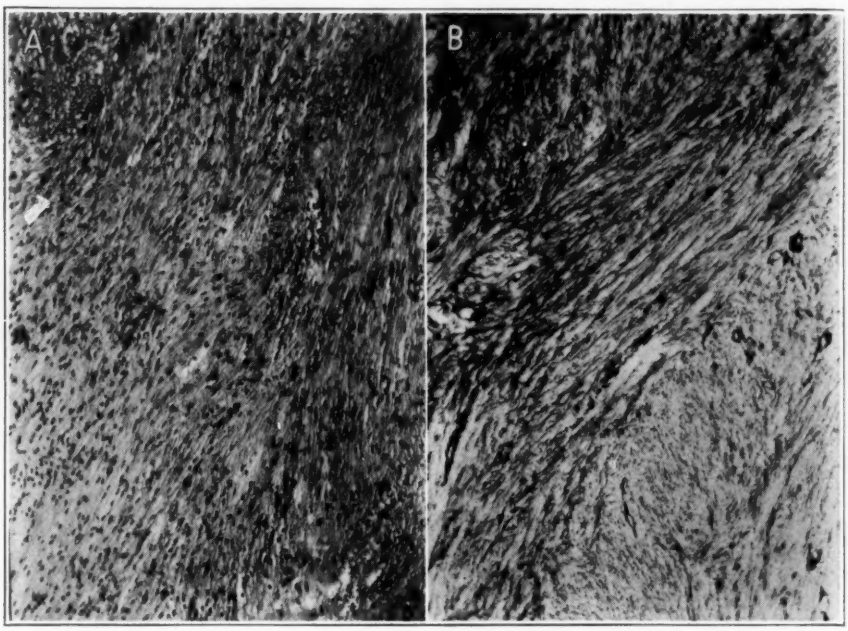

Fig. 9 (case 4, *IVB3a*).—*A*, section of the tumor showing the character of the tissue. The arrangement is less orderly, but there is a tendency toward definite streaming of the tissue elements. Hematoxylin and eosin; × about 77. *B*, section of the tumor illustrated in *A* stained to show the connective tissue. In the upper portion of the section the fibers are cut at right angles to their long axis. Perdrau stain; × about 77.

At the periphery of the tumor and in many centrally placed areas typical spindle cells in linear arrangement could be identified. The essential pattern of the tissue was readily recognizable with the Perdrau stain (fig. 9 *B*). With this method the tumor tissue was seen to contain interlacing and streaming bands of fine argentophilic fibers, typical of acoustic tumors.

This patient is the only member of the sixth generation known to be affected at present. It is probable that in the future other members of the family in her generation will present signs of acoustic tumors.

The characteristic syndrome leaves no doubt as to the presence of a tumor on the unexplored left side. It remains to be seen whether the remaining growth will progress to the point of endangering life. The palsy of the cranial nerves which followed the extensive operation necessary to remove completely the tumor on the right side makes one hesitate to undertake removal of the tumor on the left. The rapidity of growth of the tumors in this case is striking, as compared with those in case 3.

REVIEW OF LITERATURE

Although von Recklinghausen [6] pointed out that neurofibromatosis could not be considered as a purely acquired disease and Thomson [7] proved the hereditary background of this disorder, relatively few complete family histories of the central type have been described. As bilateral acoustic tumors represent a form of central neurofibromatosis, the literature on the subject is of interest. The following family histories, given briefly, have been collected from the literature. The family trees have been constructed from the data given in the reports. Dark-

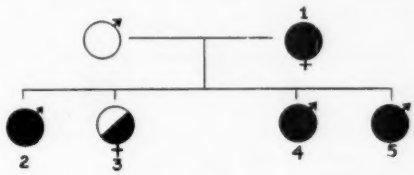

Fig. 10.—Family with neurofibromatosis reported by Struwe and Steuer.[8]

ened circles are used to indicate affected members; half-darkened circles, members probably affected, and undarkened circles, unaffected members. The numbers used to indicate cases do not in all instances correspond with those used by the authors.

Struwe and Steuer [8] reported on a family in which a mother and 4 children were affected (fig. 10).

1. The mother died at the age of 35, after having been deaf and blind. Necropsy showed extensive central neurofibromatosis with involvement of the peripheral as well as the sympathetic nervous system.

2. A son had become deaf and blind at the age of 22 years. Two large dural tumors and two large neurofibromas adjacent to the pons were observed at necropsy. There were also tumors of the peripheral nerves.

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6. von Recklinghausen, F.: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen, Berlin, A. Hirschwald, 1882.

7. Thomson, A.: On Neuroma and Neurofibromatosis, Edinburgh, Turnbull & Spears, 1900.

8. Struwe, F., and Steuer, E. J.: Eine Recklinghausen-Familie. Klinische und anatomische Untersuchungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:748-790, 1930.

3. A daughter was blind in the right eye and became partially deaf at the age of 17 years.

4. A son became deaf when 16 years old and died at the age of 29. Necropsy disclosed extensive central and peripheral neurofibromatosis.

5. A son became deaf and blind, and exophthalmos developed. He died at the age of 20.

Minski [9] reported the occurrence of 3 cases of central neurofibromatosis in one family (fig. 11). The father was alive but crippled at the age of 70, at the time of the report.

1. A woman died at the age of 41. Necropsy disclosed bilateral acoustic tumors and neurofibromas on many of the cranial nerves. There was also a small endothelioma of the dura mater in the posterior fossa. She had 3 children, none of whom were affected.

2. A man aged 34 was living at the time of writing. He had peripheral neurofibromas, bilateral deafness and tinnitus, palsies of the cranial nerves and bilateral changes in the petrous bones, as shown by roentgen examination. He had 3 children, 1 of whom was mentally defective.

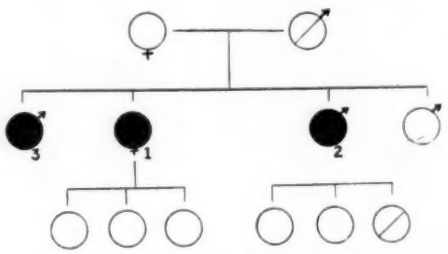

Fig. 11.—Family with neurofibromatosis reported by Minski.[9]

3. A boy died at the age of 15 years, with the clinical diagnosis of tumor of the spinal cord. Necropsy disclosed an intradural tumor of the spinal cord.

Schaltenbrand [10] described a family in which 2 members had central neurofibromatosis and 2 other members had multiple anomalies. The father died at the age of 63 of delirium tremens. The mother died at the age of 52 of unilateral epileptic attacks, during which she retained consciousness; these started immediately after childbirth (fig. 12).

1. In the case of a woman who died at the age of 35 necropsy disclosed central and peripheral neurofibromatosis with bilateral acoustic tumors and multiple intracranial meningiomas.

2. In the case of a girl who died at the age of 18 necropsy disclosed multiple intracranial meningiomas, an enormous meningioma of the falx, a glioma of the cord and tumors of the peripheral nerves.

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9. Minski, L.: Familial Bilateral Acoustic Tumours, J. Neurol. & Psychopath. **12**:289-308 (April) 1932.

10. Schaltenbrand, G.: Sobre una familia con enfermedad de Recklinghausen, Prensa méd. argent. **20**:1011-1026 (May 10) 1933.

3 and *4*. Two other members of the family were affected with multiple anomalies, but neither showed definite evidence of Recklinghausen's disease. One, a girl aged 9 years (*3*), had chorioretinitis and enlargement of the heart, with a diffuse systolic murmur. The other, a boy aged 13 years (*4*), had an area of anesthesia over the right calf, tremor of the eyelids, severe myopia, nystagmus on left lateral gaze and an albino fundus in the left eye.

Roger, Alliez and Sarradon [11] described a family in which the disease had been transmitted through three generations and had affected 5 members (fig. 13).

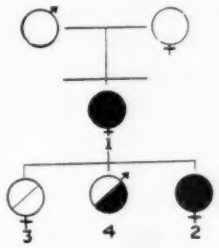

Fig. 12.—Family with neurofibromatosis reported by Schaltenbrand.[10]

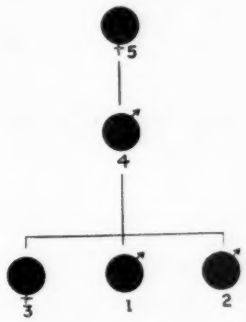

Fig. 13.—Family with neurofibromatosis reported by Roger, Alliez and Sarradon.[11]

1. A man aged 53, who died with all the symptoms of bilateral acoustic tumors, at necropsy was observed to have bilateral acoustic tumors and peripheral neurofibromatosis.

2. A man, who died at the age of 29, had bilateral blindness with optic atrophy, unsteadiness of gait, dysarthia and loss of the sense of taste. Necropsy disclosed marked hydrocephalus and a tumor in the left cerebellopontile angle, which was diagnosed as a "fibromyxosarcoma."

3. A woman died of a tumor of the brain after simple decompression. No necropsy was performed.

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11. Roger, H.; Alliez, J., and Sarradon, P.: Tumeur bilatérale de l'acoustique à forme familiale et héréditaire, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:235-240 (Feb. 19) 1934.

4. The father of the preceding 3 patients died at the age of 45. He was deaf, had visual impairment and difficulty in walking and became paralyzed before death. No operation or necropsy was performed.

5. The mother of patient *4* died after presenting symptoms similar to those of her son.

Stallard [12] described a case of intraocular neuroma in which there was a history that 5 other members of the family gave evidence of having had some form of central neurofibromatosis. Three generations of the family were affected at the time of the report (fig. 14).

1. A man had been subject to epileptic fits in his youth. He died at the age of 49, after having become deaf, blind and paralyzed.

2. A man, one of twins, became deaf and ataxic at the age of 29 and died when 30½ years old, after having become paralyzed. His twin died at the age of a few months.

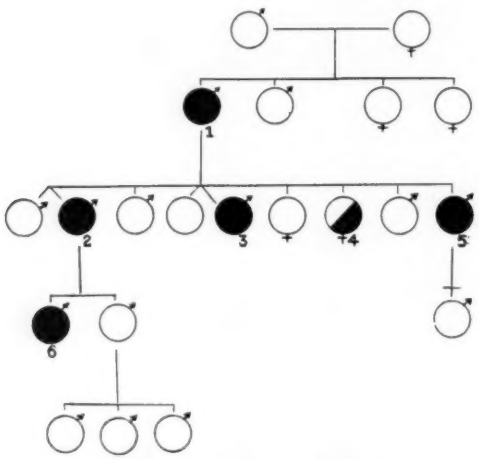

Fig. 14.—Family with neurofibromatosis reported by Stallard.[12]

3. A man whose hearing, sight and speech failed at the age of 14 years died at the age of 22½, after progression of symptoms.

4. A girl died at the age of 18½ years, after an intracranial operation.

5. A man became blind, ataxic and deaf at 37 years of age. He died a year and a half later, after an intracranial operation. He had 1 son, who at the age of 6 was not affected.

6. A man, aged 22 at the time of his death, had had a "neuroma" of the left eye at the age of 19, for which the globe was enucleated. Unsteadiness of gait, auditory impairment, blurred vision in the remaining eye and severe headaches, with deafness and marked ataxia, gradually developed. Projectile vomiting occurred, and the patient died immediately after a suboccipital exploration. Necropsy was not performed.

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12. Stallard, H. B.: A Case of Intra-Ocular Neuroma (von Recklinghausen's Disease) of the Left Optic Nerve Head, Brit. J. Ophth. **22**:11-18 (Jan.) 1938.

We [13] described a family in which multiple tumors of the enveloping membranes and sheaths of the nervous system were present in 5 members of the family. Two other members gave evidence of involvement. Three generations of the family were represented (fig. 15).

1. A woman had "lumps" in her skin and became blind and paralyzed before her death.

2. In the case of a woman who died at the age of 32 necropsy revealed bilateral acoustic tumors and multiple intracranial and intraspinal meningiomas and neurofibromas, as well as intramedullary gliomas.

3. In the case of a woman aged 39 at the time of her death necropsy revealed bilateral acoustic tumors and multiple intracranial neurofibromas and meningiomas.

4. In the case of a girl aged 11 years examination revealed multiple tumors of the skin but no definite evidence of intracranial growths.

5. A girl aged 9 years had multiple tumors of the skin but no definite evidence of intracranial tumors.

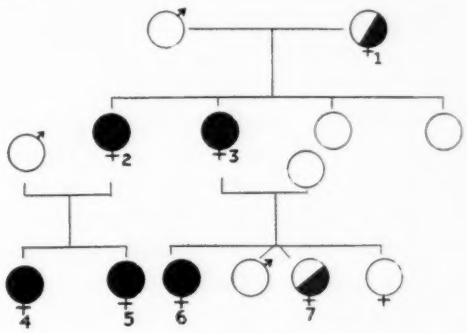

Fig. 15.—Family with neurofibromatosis reported by Turner and Gardner.[13]

6. A girl aged 8 years had signs of intracranial tumor but no peripheral lesions. Necropsy disclosed a large meningeal tumor on the left, which extended from the orbit, where it had caused exophthalmos, to the subtentorial region, where it compressed the cerebellum.

7. A girl aged 10 presented weakness of the right side of the face and complete blindness in the right eye. There were no peripheral tumors. The clinical diagnosis was early central neurofibromatosis.

COMMENT

There has been no evidence that single acoustic tumors, in the absence of the more usual signs of Recklinghausen's disease, represent a form of neurofibromatosis. These solitary growths have never been known to exhibit familial tendencies. While the microscopic picture often resembles that of the neurofibroma, there are definite and char-

13. Turner, O. A., and Gardner, W. J.: Familial Involvement of the Nervous System by Multiple Tumors of the Sheaths and Enveloping Membranes: Hereditary, Clinical and Pathological Study of Central and Peripheral Neurofibromatosis, Am. J. Cancer **32**:339-360 (March) 1938.

acteristic differences between the two.[14] Nevertheless, it is possible, as Cushing and Eisenhardt [4] have pointed out, that single acoustic tumors, bilateral acoustic tumors and generalized involvement of the central nervous system represent merely gradations of the same disorder and not different diseases. While work has been done on the last two forms, there still remains to be investigated the relationship of the single acoustic tumor to Recklinghausen's disease. Although the family described here indicates that bilateral acoustic tumors may be transmitted as an "incomplete" form of Recklinghausen's disease, one must not be too ready to assume that the nonhereditary single acoustic tumors are an "abortive" or "frustrated" central form of the malady.

There has been considerable work to show that the form of Recklinghausen's disease occurring in the central nervous system may be transmitted as a dominant mendelian trait, often without the usual peripheral manifestations. The particular character of the disease process in individual cases or families varies considerably, but in most instances the neurofibromatous background of the process is easily recognized. The particular pathologic picture in any isolated case depends on the stage to which the disease in that instance has developed. Aside from the age of the patient, i. e., the length of time the disease has been present, certain other factors are apparently involved. In the original article by Gardner and Frazier [1] it was pointed out that the condition was increasing in malignancy as transmission proceeded. This was indicated by the shortening of the life span of affected members in successive generations.

The fact that 2 members of the family had tumors other than bilateral acoustic neurofibromas indicates that this condition is not a final stage in the development of the disease process in this family. In the light of these 2 cases it seems likely that more diffuse involvement may develop in other affected members. However, whatever progression there is may require passage through several more generations. There is no apparent explanation for the manner in which the disease in this family has evolved to the occurrence of bilateral acoustic tumors, with little tendency toward more diffuse involvement of the nervous system. The natural history of the disease, when it affects the central nervous system, is toward rapid and widespread involvement of all the sheaths and enveloping membranes.[15] This is true in cases of the isolated growth as well as in those of the familial form. In the case reported by Berg-

14. Penfield, W.: Tumors of the Sheaths of the Nervous System, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, pp. 955-990.

15. Footnote deleted.

grün [16] there were multiple bilateral tumors of the cranial nerves in a child aged 11 years. In the family reported by us,[13] the oldest patient was 39, and necropsy showed multiple tumors of the dura, cranial nerves and spinal cord. The present family is the only one in which the essential form of the disorder is limited to bilateral acoustic neurofibromas.

With regard to the members of the family reported here, little additional comment is required. Each case presents certain interesting characteristics, to which reference has already been made. Certainly, the relationship between the meningeal tumor and the tumor of the right acoustic nerve in case 1 is unusual, and to our knowledge such a case has not been reported heretofore. Similarly, the long duration of the symptoms in case 3 and the disclosure of bilateral tumors, 1.0 and 1.5 cm., respectively, in diameter, is rare. To our knowledge they are the smallest bilateral acoustic tumors described. From the work of Hardy and Crowe [17] and Fowler [18] it seems likely that other members of the family may have still smaller, asymptomatic acoustic tumors.

SUMMARY

In 1930, Gardner and Frazier reported a family in which Recklinghausen's disease, in the form of bilateral acoustic tumors, had been transmitted as a dominant mendelian trait through five generations. At that time the diagnosis was verified histologically in only 2 cases, although the evidence indicated that 38 members were affected.

The present report summarizes the earlier description of this family and brings it up to date. The gross and histologic observations in the cases of 4 additional affected members are described. One of the cases occurred in the sixth generation of this family.

Several published reports of familial central neurofibromatosis are summarized.

Staff members of the Geisinger Memorial Hospital, Danville, Pa., assisted in carrying out postmortem examinations on several members of the family. Dr. Allen Graham, of the department of pathology of the Cleveland Clinic Foundation Hospital, prepared many of the tissue sections and photographs. Dr. Louise Eisenhardt assisted in interpreting several of the tumor sections and Dr. David Masson aided in translating some of the foreign articles.

16. Berggrün, E.: Ein Fall von allgemeiner Neurofibromatose bei einem 11jährigen Knaben, Arch. f. Kinderh. **21**:89-113, 1896.

17. Hardy, M., and Crowe, S. J.: Early Asymptomatic Acoustic Tumor: Report of Six Cases, Arch. Surg. **32**:292-301 (Feb.) 1936.

18. Fowler, E. P.: Acoustic Tumors Within Internal Auditory Meatus, Laryngoscope **46**:616-627 (Aug.) 1936.

INNERVATION OF ANNULUS FIBROSUS AND POSTERIOR LONGITUDINAL LIGAMENT

FOURTH AND FIFTH LUMBAR LEVEL

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The object of this report is to record observations on the innervation of the annulus fibrosus and the posterior longitudinal ligament at the fourth and fifth lumbar level. Recent reports in the literature concerning clinical cases of severe pain in the lower part of the back caused by herniation of the nucleus pulposus without peripheral disturbance aroused my interest in investigating the position and type of fibers involved in transmitting the pain impulse. Spurling and Bradford [1] reported that in many cases in which the herniation has remained in the midline, not sliding down along the dural sleeve of the nerve, there is localized pain of great intensity. The most frequent level at which such herniations occur is between the fourth and the fifth lumbar vertebra. Localization of pain may occur at any level at which such a herniation appears.

The question whether the nerves involved are related directly to the annulus fibrosus, the posterior longitudinal ligament, the periosteum, the perichondrium or blood vessels which form a rich plexus in the vertebral canal is not solved from what is known of the nature of localized pain in these regions, but it seems most likely that the fibers to the annulus fibrosus are responsible. Further detailed study is necessary.

Jung and Brunschwig [2] demonstrated unmyelinated nerve fibers in the anterior longitudinal ligament, but found none in the disks themselves. They noted few in the lateral and posterior longitudinal ligaments and did not mention the innervation of the annulus fibrosus. Leriche [3] stressed the importance of the innervation of the vertebral articulations.

From the Department of Anatomy, University of Louisville School of Medicine.

1. Spurling, R. G., and Bradford, F. K.: Neurological Aspects of Herniated Nucleus Pulposus at the Fourth and Fifth Lumbar Interspaces, J. A. M. A. **113**: 2019 (Dec. 2) 1939.

2. Jung, A., and Brunschwig, A.: Recherches histologiques sur l'innervation des articulations des corps vertébraux, Presse méd. **40**:316 (Feb.) 1932.

3. Leriche, R.: Recherches sur le rôle de l'innervation sensitive des articulations et de leur appareil ligamentaire dans la physiologie pathologique articulaire, Presse méd. **38**:417 (March) 1930.

The origin of the fibers which carry pain impulses from the vertebral articular ligaments is unknown. If they are somatic, they may have two recurrent routes: (*a*) direct return to the canal through the intervertebral foramen or (*b*) the recurrent branch diagramatically illustrated in Gray's "Anatomy." If of visceral origin they are related to blood vessels. The presence and distribution of nerves innervating all the vertebral articulations constitute a problem now under investigation in this laboratory.

MATERIALS AND METHODS

Tissues for study were obtained at autopsies and laminectomies. Six autopsy specimens of the posterior longitudinal ligament and annulus fibrosus from men ranging in age from 50 to 67 and 1 autopsy specimen from a girl aged 2 years were fixed in the following solution: glacial acetic acid, 5 cc.; solution of formaldehyde U. S. P. (commercial), 5 cc.; 80 per cent alcohol, 90 cc. They were embedded in pyroxylin, sectioned horizontally at 20 to 35 microns and stained by Bodian's [4] activated strong protein silver–reduced silver method. Two specimens from men were removed at laminectomy and treated immediately by the gold chloride method of Garven.[5]

In the case of the autopsy material the bodies of the fourth and fifth lumbar vertebrae were removed with the intervening disk and the accompanying posterior longitudinal ligament. This large mass was fixed in the aforementioned solution, and the soft tissues were later removed for study. The material from the laminectomies was removed by Dr. R. Glen Spurling from the region between the fourth and the fifth lumbar vertebra.

An attempt was made to trace the origin of nerves which were observed to innervate the annulus fibrosus and the posterior longitudinal ligament. Careful dissection in a cadaver of recurrent spinal nerves to the aforenamed structures revealed fibrous-like strands returning from beyond the dorsal root ganglia to the vertebral canal through the intervertebral foramen. Histologic examination of these strands was not convincing as to whether they were nerve fibers. Nerves from a recurrent branch other than one passing through the intervertebral foramen were not seen in the cadaver. A more careful investigation of the origin of these fibers is under way.

RESULTS

Many unmyelinated nerve fibers were observed in the tissue of the annulus fibrosus. In the accompanying figure a photomicrograph of teased material from the annulus fibrosus, prepared by Garven's gold chloride method, a small bundle made up of several fibers is shown. These fibers terminated in naked nerve endings within the annulus; no nerve tissue was observed within the disk itself. The fibers were very fine and unmyelinated.

4. Bodian, D.: The Staining of Paraffin Sections of Nervous Tissues with Activated Protargol: The Rôle of the Fixatives, Anat. Rec. **69**:153 (Sept.) 1937.

5. Garven, H. S. D.: The Nerve-Endings in the Panniculus Carnosus of the Hedgehog, with Special Reference to the Sympathetic Innervation of Striated Muscle, Brain **48**:380, 1925.

In the posterior longitudinal ligament a small number of fine unmyelinated fibers were observed. Their position almost invariably was near the annulus fibrosus, in an area where the posterior longitudinal ligament fans out to merge with the annulus fibrosus. These fibers were impregnated by Bodian's activated strong protein silver–reduced silver method. They showed naked nerve endings as well as glomerulus-like terminations. A few nerve fibers were seen associated with blood vessels, but in no case were the nerve fibers of the ligament observed in connection with the nerves of blood vessels.

COMMENT

The presence of nerve fibers within the tissue of the annulus fibrosus gives substantial physical evidence of the basis of localized pain. This

Photomicrograph of a teased preparation of tissue from the annulus fibrosus stained by the gold chloride method of Garven. The darkly stained bundle of unmyelinated nerve fibers overlies the fibrous material of the annulus. × 145.

report concerns itself exclusively with the fourth and fifth lumbar intervertebral area, but it is assumed that other areas are similarly innervated; at least the reports of clinical cases in the literature would lead one to that opinion. At what level the fibers arise is still undetermined, but from the little evidence at hand the fibers innervating the area between the fourth and the fifth lumbar area arise from the third or the fourth lumbar nerve. The exact course of nerve fibers innervating the ligaments of the spinal column is still to be determined.

No attempt was made to study the innervation of the lateral or the anterior longitudinal ligaments of the spinal column. The work of Jung and Brunschwig already cited adequately presents this subject.

SUMMARY

The annulus fibrosus and the posterior longitudinal ligament between the fourth and the fifth lumbar vertebra are innervated by fine unmyelinated nerve fibers. Their exact origin and course were not determined. The fibers end in naked nerve endings in the annulus fibrosus, and in like manner in the posterior longitudinal ligament with glomerulus-like terminations as well.

PRIMARY MELANOTIC TUMORS OF THE MENINGES: RESEMBLANCE TO MENINGIOMAS

REPORT OF TWO CASES IN WHICH OPERATION WAS PERFORMED

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Primary melanotic tumors of the central nervous system are rare, and reports of no more than 30 cases have appeared in the literature. Even some of these are open to question because of the possibility that the tumors were secondary to some unrecognized origin elsewhere in the body. However, there appears to be substantial reason to assume that these tumors can arise in the meninges of the brain and cord.

The great majority of cases reported have tended to conform, more or less, in that the tumors originated in the leptomeninges, invaded the adjacent neural parenchyma and spread along the subarachnoid spaces after the fashion of meningitis, ending in death in less than two years after the onset of symptoms.

We have encountered at the New York Hospital 2 cases of primary melanotic tumor of the meninges—1 of spinal and 1 of cranial tumor. The growths were decidedly unlike those previously described in both their gross and their microscopic characteristics. Both patients have been operated on and are living and well four years and one and one-half years after operation respectively.[1] We have been impressed by the striking similarity between the two tumors and the common meningiomas and believe that a report of the cases may serve to advance knowledge about melanotic tumors of the meninges and, perhaps, establish a relation with the meningiomas.

REPORT OF CASES

CASE 1 (Spinal Tumor).—*Pain radiating from the lower part of the back down both lower extremities and occasional paresthesias in these extremities for five years; minimal neurologic signs indicating a lesion of the cauda equina, but*

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1. Both patients were well five years and two years respectively after operation when last examined, July 1, 1940.

spinal fluid picture indicative of a block of the spinal canal; surgical removal of a melanotic tumor arising from the meninges; four year cure.

History.—May F., a housewife aged 29, was admitted to the New York Hospital on Sept. 10, 1935, having been referred by Dr. James A. Cooley. On the day after the birth of a baby five years previously she had first experienced a "pain like a toothache" beginning in the left lower part of the back and extending to the left gluteal region, the outer aspect of the thigh and the shin. She had never been entirely free of this pain thereafter, and in the last three years there had developed a similar, though less severe, pain in comparable areas on the right side. She was least comfortable when walking or lying in bed and most comfortable when sitting in a chair or relaxing in a warm bath. Sneezing and other straining produced excruciating pain in the lower part of the back. On several occasions after exertion

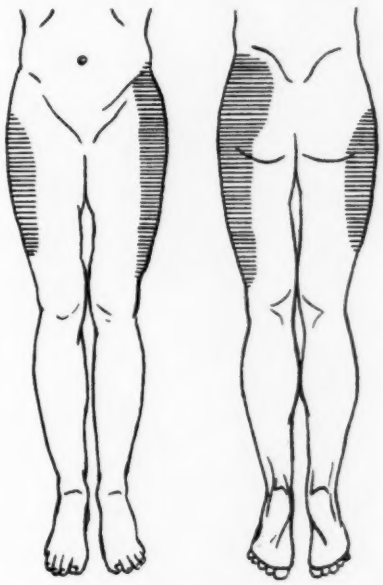

Fig. 1 (case 1).—Diagram of the sensory changes. Areas of impaired sensitivity to touch and pinprick are represented by shading.

she had experienced a transitory numb and tingling sensation in both lower extremities. She denied any feeling of weakness in the extremities or disturbance of function of the bladder or of the bowel. Braces, supporters and various forms of physical therapy had all failed to give relief.

Examination.—The patient was well developed and appeared healthy. The general physical findings were not remarkable. She showed no evidence of a reported loss of 10 pounds (4.5 Kg.) in weight. Her general complexion was medium dark, and there were a few small, pale freckles on the body, principally on the exposed parts. Aside from the neurologic changes there were no remarkable physical abnormalities.

The neurologic findings were normal except for the lower extremities. No wasting of the muscles of the lower extremities, no fibrillary twitchings and no

apparent change in strength or tonicity were observed. Both knee jerks were present, the left brisk and the right sluggish; the ankle jerks were also present, the right normal and the left sluggish. Sensation was markedly impaired over the outer aspect of the left thigh and to a lesser degree over a similar area of the right thigh (fig. 1). Roentgenograms of the lower segments of the spine failed to show any abnormality. Lumbar puncture in the fourth interspace indicated complete block of the spinal canal and yielded 2 cc. of xanthochromic fluid. No unusual cells were seen in this fluid.

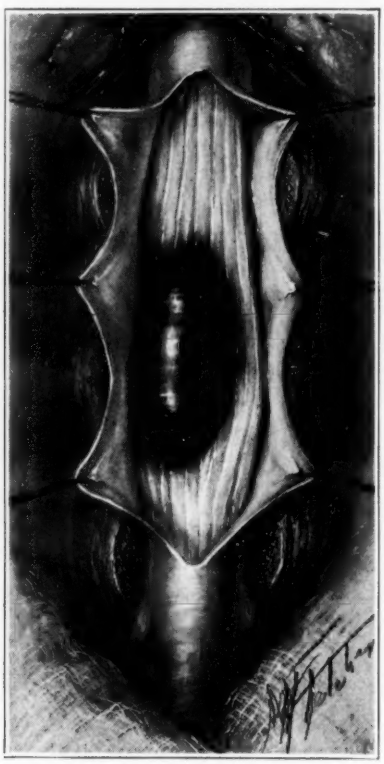

Fig. 2.—Appearance of the spinal tumor at operation.

Operation.—On September 26, with the patient under ether anesthesia, laminectomy of the first, second and third lumbar vertebrae, was performed. There was no indication of a tumor until the dura was opened, but then there appeared at the level of the third lamina a well encapsulated, shiny, purplish black tumor measuring 1.5 by 1 by 3.5 cm. (fig. 2). There had been a few flimsy adhesions between the tumor and the reflected dura, but the principal attachment was a comparatively small pedicle at the point of emergence of the third lumbar nerve on the left. Other nerves of the cauda equina had been distorted by the tumor, but none of them were attached to it. To remove the pedicle completely it was necessary to resect a segment of the nerve and a small segment of dura. Hemostasis presented no problem, and the wound was closed with silk.

Pathologic Picture.—The capsule was thin, and compression of the tumor easily ruptured it. A mass of tarry, black putty-like material was extruded. Some of the material was semiliquid, but the rest was soft and plastic.

Microscopic sections (fig. 3) showed the tumor to have a spongy or breadlike makeup. The cells were arranged around channels that sometimes contained blood and sometimes held coagulated lymph but were usually empty. The cells were in interlacing bundles as a rule, but here and there they formed well defined whorls. They were rather small, regular in shape and often slightly stellate, with radiating processes. They resembled the teased cells of meningiomas; like these they anastomosed with one another. Typed by the Cushing list they would have fallen into type 1, variant 3, or possibly into type 5, variant 1. Unlike the latter, however, mitotic figures were not present as far as could be made out after repeated and thorough search. All these cells contained melanin in good quantity, usually

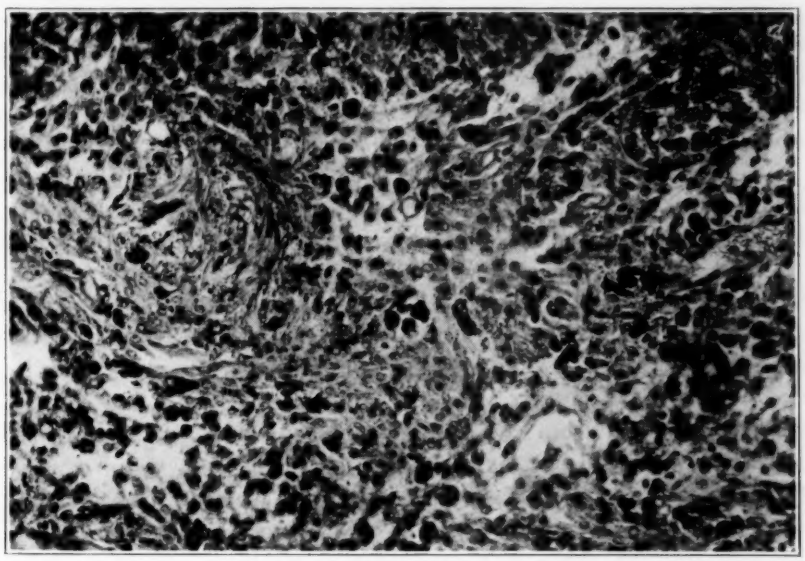

Fig. 3.—Photomicrograph of the spinal tumor. Note the whorled areas in the tumor and the resemblance of the cellular arrangement to that of meningioma. Pigmentation is rather marked and generalized. Masson's stain; × 170.

finely divided but sometimes in rather coarse granules. The nuclei were rather dark, with small and numerous karyosomes and occasional blue-staining and distinct nucleoli. These nuclei resembled those of the meningiomas in every respect. The stroma of the neoplasm was scanty and predominantly reticular. Reticulum did not run among the tumor cells, however, but was limited to the stroma and the immediate vicinity of the vessels. Here there were chromatophores loaded with melanin, but they were almost invariably globular.

Diagnosis.—The diagnosis was melanotic tumor, primary in the meninges.

Postoperative Course.—Recovery from operation was rapid, and when the patient left the hospital three weeks later she was entirely free of pain; reflexes and motility functions were unchanged; there was an area of anesthesia over the outer aspect of the left thigh.

Follow-Up.—She has been examined numerous times in the ensuing four years, since operation and has consistently been free of complaints. At the time of writing, muscle power and reflexes in the lower extremities are normal. There remains an area of permanent anesthesia over the outer aspect of the left thigh; otherwise sensation is normal. There have been no changes in the pigmentation of the skin; the liver is not palpable, and the eyegrounds are normal.

Comment.—From the history of this case there is every reason to believe that the tumor had been present for at least five years prior to operation, so that it must have been growing slowly. When exposed at operation it aroused passing interest because of its color, but in every other respect was like a meningioma or a tumor of the sheath of Schwann (lemmoma). Its comparatively small attachment was to all layers of the meninges at the point of emergence of a nerve root, and it was necessary in its removal to resect the nerve as well as a small fragment of dura. There was no pigmentation or unusual appearance of the other structures in the region to suggest that the tumor had spread beyond the confines of its capsule and base.

With the outstanding exceptions of several cases, the primary melanomas of the spinal meninges described in the literature have all, sooner or later, been diffuse malignant tumors spreading along the pia-arachnoid, sometimes invading the parenchyma but avoiding the dura. In the 3 cases reported by Boit,[1a] Kawashima [2] and Lindbom,[3] encapsulated, discrete melanotic tumors are said to have arisen primarily from the spinal dura and to have compressed the cord without invading it; within two years after the onset of symptoms, all 3 patients died without operation from complications of transverse myelitis. In the cases reported by Kawashima [2] and by Lindbom [3] the descriptions of the tumor's attachment indicate that in each case it arose from the dura at the point of emergence of a nerve root but that, in addition (and this suggests that the origin may have been from the leptomeninges after all), the pia covering the adjacent segments of the cord in each case was pigmented. These points are stressed because the possibility of the origin of melanoma from the pia-arachnoid is now fairly well established, whereas its origin from the dura alone seems unlikely. More difficult to accept is Boit's [1a] case, in which the tumor, thought to arise from the spinal dura, was attached only to its outer surface; none of the subdural structures were invaded. An almost identical tumor was described by

1a. Boit, H.: Ein Fall von Chromatophoroma dura matris spinalis: Beitrag zur Kenntnis des Chromatophoroma piale, Frankfurt. Ztschr. f. Path. **1**:248, 1907.

2. Kawashima, K.: Ueber ein Sarkom der Dura mater spinalis und dessen Dissemination im Meningealraum mit diffuser Pigmentation der Leptomeningen, Virchows Arch. f. path. Anat. **201**:297, 1910.

3. Lindbom, O.: A Case of Chromatophoroma Durae Matris Spinalis, Hygiea **74**:198, 1912.

Elsberg;[4] the patient was subsequently found to have had a melanosarcoma of the eye.

In our case, in addition to the long preoperative duration of the disease and the tumor's other gross characteristics of meningioma or lemmoma, there is the cellular resemblance, particularly to the former. Others have been impressed by the cellular similarity, and in the case reported by Schnitker and Ayer[5] the tumor surgically removed from the cord was diagnosed as "atypical meningioma"; only on examination of the autopsy tissue was the diagnosis of melanoma established. That intraspinal meningiomas and neurinomas (lemmomas) are somehow related and often difficult to differentiate has been made the subject of a chapter in Cushing and Eisenhardt's[6] recent monograph, "Meningiomas." It seems but a simple additional step to add melanomas to the family.

The tumor in our case was thought to have been totally removed. Because of its cellular nature and the reputation of melanotic tumors, it is perhaps unwise to consider it nonmalignant. On the other hand, because of the absence of mitotic figures and the tendency for the tumor to break down, plus the long postoperative period without evidence of recurrence, there is certainly reasonable likelihood of a cure. The total period which has elapsed between the onset of symptoms and the time of this report is nine years, and if some other primary lesion exists it should long since have come to light.

It was many months after encountering the unusual tumor of the spinal meninges that we met with a bizarre melanotic tumor of the cranial meninges and came to realize the necessity of giving some consideration to the nature of the pigmented tumors of the nervous system.

CASE 2 (Cranial Tumor).—*Headache, vomiting, olfactory hallucinations, unsteady gait, failing vision, convulsions and stupor progressively appearing within a year; signs of intracranial tumor without localization; ventriculogram; suboccipital exploration; partial removal of a primary melanotic tumor arising from the meninges; roentgen irradiation; complete recovery without return of symptoms after one and one-half years.*

History.—Mary McM., an American housewife aged 45, was admitted to the hospital on April 13, 1938, having been referred by Dr. William Jessup. She had had progressively frequent and severe frontal and suboccipital headaches which had started a year before and had continued up to the time of admission. Vomiting had been a more recent development and characteristically occurred when the head-

4. Elsberg, C. A.: Tumors of the Spinal Cord [case 60], New York, Paul B. Hoeber, 1925, p. 179.

5. Schnitker, M. T., and Ayer, D.: Primary Melanomas of the Leptomeninges: Clinico-Pathologic Study with Review of the Literature and Report of an Additional Case, J. Nerv. & Ment. Dis. **87**:45-73, 1938.

6. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C. Thomas, Publisher, 1938, chap. 4.

aches were most severe. Vision had become gradually blurred during this period, and there were fleeting periods of amaurosis. Walking had been noticeably unsteady for at least six months, and often there was tremor of the hands. Unpleasant and persistent odors had unaccountably appeared on numerous occasions for several months. Finally, several days before admission, she had had three attacks characterized by loss of consciousness and convulsive movements of the face. These marked the onset of increasing mental sluggishness and finally of stupor (by the time of admission).

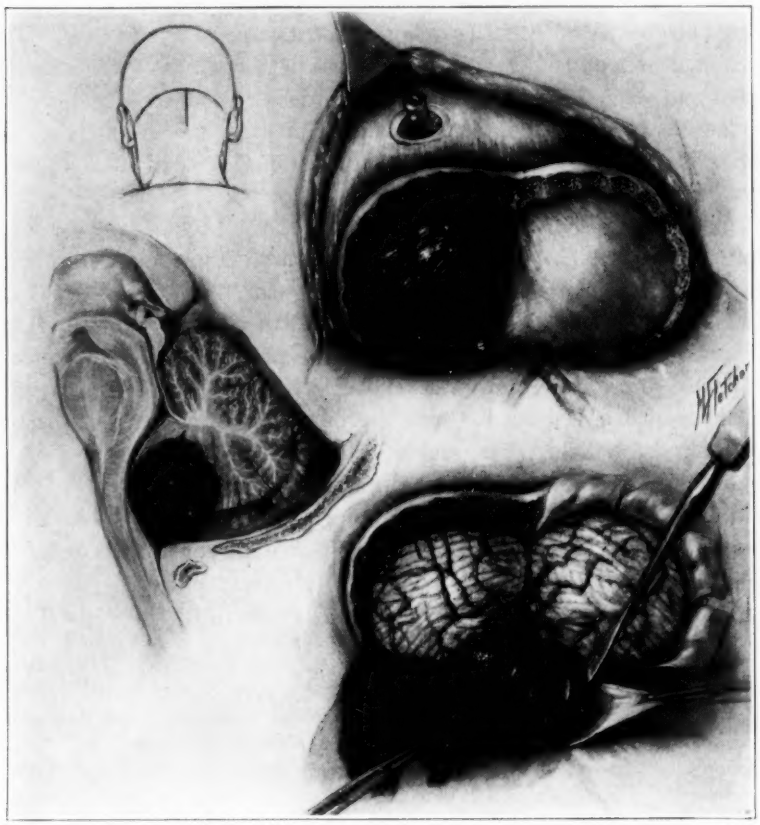

Fig. 4.—Appearance of the cranial tumor at operation. Note the pigmentation of the bone and of the dura on the left side.

Examination.—The patient was slightly obese, with good physical development. Her complexion was medium dark, and there were many light freckles about the shoulders and arms, with fewer about the face and other parts of the body; there were no other pigmented areas. Aside from the neurologic changes there were no remarkable physical findings.

The patient was lethargic in action and slow to respond to questioning; her attention lapsed easily, and occasionally she would talk confusedly. Many tests requiring cooperation gave unreliable results, but both pupils were dilated; there were bilateral choking of the disks (3 D.), with fresh hemorrhages, and weakness of

the left side of the face. Turning the head and flexing the neck were resisted and elicited local pain. Pressure in the suboccipital region on both sides was painful also. There were slight increase to passive stretch of all extremities and a coarse tremor of both upper extremities. All deep reflexes were brisk and equal. The abdominal reflexes were sluggish and exhaustible; the right plantar reflex was equivocal, but the left was abnormal. There was bilateral ankle clonus, more marked on the left. Sensation was normal. Roentgenograms of the skull showed thinning of the bones and erosion of the clinoid processes. The pineal gland was not displaced. Ventriculograms showed a markedly dilated ventricular system and a block at the fourth ventricle.

Operation.—On April 18, with the region under local anesthesia, exposure was made of the posterior fossa (fig. 4) with the patient in the prone position. The cancellous part of the occipital bone on the left side contained a dark pigment, but the appearance and consistency of the bone was otherwise unchanged. The dura on the left side was slightly more adherent to the bone and had a coal black appearance; the pigmentation stopped abruptly at the midline, and the dura on the right was normal. As the dura was reflected toward the foramen magnum, a black, firm, encapsulated tumor nodule was observed filling the region of the cisterna magna. The nodule had not visibly invaded the pia or the parenchyma but had merely displaced the cerebellum and compressed the medulla; its attachment was to the dura at the left superior rim of the foramen magnum, and the base was about 1.5 cm. in diameter. All of the exposed pigmented dura was excised together with the nodule, but much of the remaining dura on the left side was pigmented. This was demonstrated by lifting up the cerebellar lobe and exposing the floor of the fossa. At no point, however, could pigment be seen on the surfaces of the cerebellum or the brain stem.

Direct Roentgen Irradiation.—After removal of the nodule and resection of the dura, 2,000 roentgen units at 90 kilovolts peak and at a distance of 20 cm. was administered to the entire exposed area of the brain before the wound was closed.

Pathologic Picture.—The specimen consisted of a tumor nodule weighing 25 Gm., a strip of dura and fragments of bone. The tumor had a thin but tough capsule; its contents were dead black to sepia and varied in consistency from mushy to putty-like. The dura, partly attached to the nodule, was darkly pigmented and moderately thickened. The fragments of bone showed dark brown to black pigmentation, principally of the cancellous parts.

Microscopic sections of the tumor nodule (figs. 5 and 6) had a surprisingly close resemblance to a meningioma of Cushing's type 1, combining features of variants 2 and 3. It was seen to be composed of fusiform or polyhedral cells that tended to form bands and whorls, in a few areas forming sheets of cells. The cells paralleled one another in the bundles and had a concentric arrangement in the whorls, often surrounding blood vessels but sometimes showing none at the center. Occasionally the cells were arranged transversely, in columns like bricks piled on their long sides. In a few areas there was palisading of the nuclei in transverse ranks, giving the appearance of typical "Verocay bodies," such as one sees in lemmomas.

The cells themselves were fusiform or polyhedral and remarkably uniform in size and shape. They often resembled the meningocytes observed in teased preparations or in tissue cultures. Such cells had a globular body, with a few processes which sometimes extended a short distance to end bluntly in a small knob or to anastomose with another cell. The nuclei were ovoid and slightly vesicular and possessed large nucleoli which stained brilliantly red in Masson sections. No mitoses

were observed. The cytoplasm was reasonably dense and quite filled with finely divided granules of melanin. Sometimes larger granules were seen, clumped within the cytoplasm in vacuoles. The stroma of the tumor was scanty, largely made up

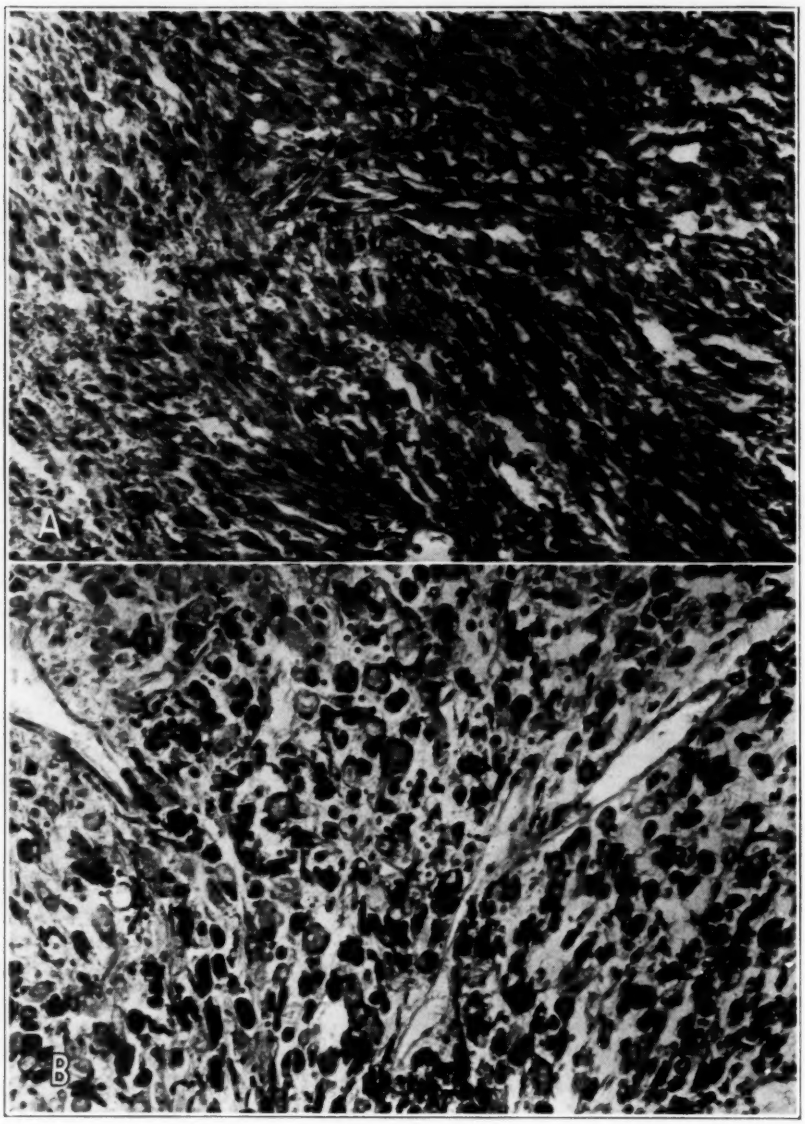

Fig. 5.—*A*, photomicrograph of the cranial tumor nodule. Note the fasciculated and slightly pigmented areas and the resemblance of the cellular arrangement to that of meningioma. Masson's stain; × 170. *B*, another photomicrograph of the cranial tumor nodule. Note the densely pigmented area. These cells lie in the stroma of connective tissue. Masson's stain; × 170.

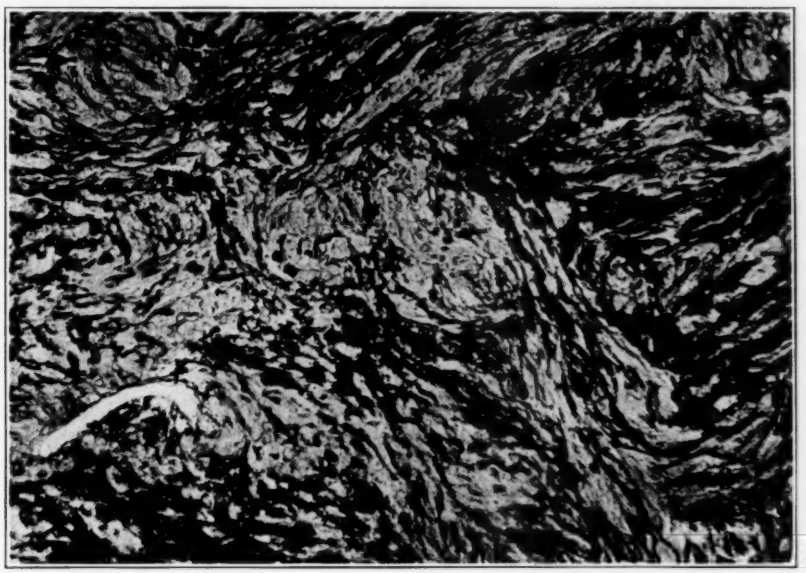

Fig. 6.—A third photomicrograph of the cranial tumor nodule. Note the extensive pigmentation demonstrable with the Cajal silver impregnation. × 170.

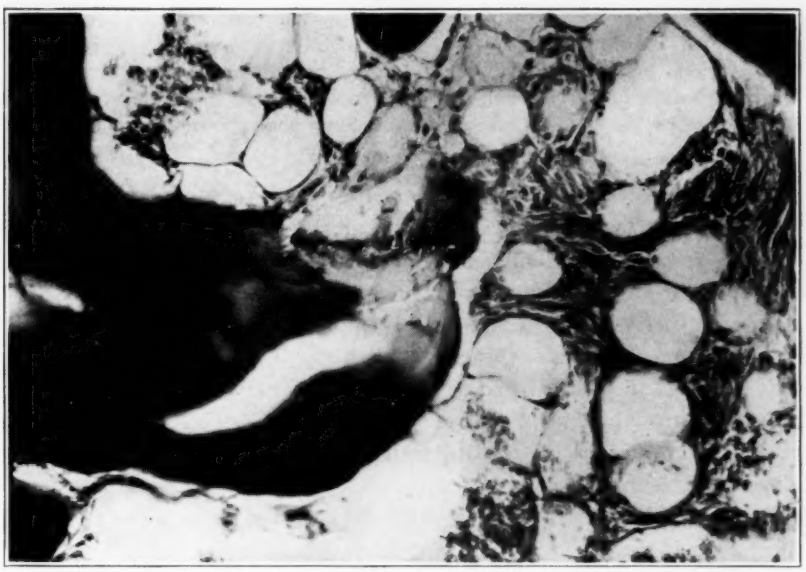

Fig. 7.—Photomicrograph of the occipital bone invaded by tumor. Note the invasion of the marrow and the erosion of the tip of a cancellous spicule. Masson's stain; × 170.

of reticulum but having some coarser collagen fibers here and there. Among these were large and prominent, usually fusiform but occasionally globular, phagocytes, literally stuffed with coarse melanin granules; these might be said to represent chromatophores rather than tumor cells. Impregnation of the tissue by a modification of Ramón y Cajal's silver nitrate method brought out the cellular morphologic structure of the tumor most strikingly and revealed the longer and shorter cell processes filled with melanin granules blackened by the silver.

Microscopic examination of the bone fragments (fig. 7) showed them to be invaded by masses of pigmented tumor cells that lay in the haversian canals in the vicinity of the blood vessels. The cells were possibly smaller and better differentiated than those of the primary tumor of the meninges and showed no mitotic activity. The bone itself was neither destroyed nor stimulated to overgrowth; it was merely passively invaded. The tumor here, as at its original site, produced pigment and reticulum. Its spread into the haversian systems of the invaded bone was in every way similar to that of those meningiomas that invade bone, the so-called osteogenic meningiomas, the highly invasive character of which produces a mass of tumor tissue that naturally increases the thickness of the bone by extending and expanding its tumor-filled haversian canals.

Postoperative Course.—Recovery from operation was prompt, and the preoperative symptoms subsided rapidly. The patient sat up on the sixteenth postoperative day and walked by the twentieth day. The choked disks subsided rapidly, and additional roentgen therapy (4,200 roentgen units administered to the suboccipital region) was given before her discharge on the thirty-third postoperative day.

Follow-Up.—The patient has reported every six months for examination. Up to the time of writing she has been absolutely free of complaint, and all the neurologic findings have remained normal. Lumbar puncture on June 21, 1939 yielded fluid under normal pressure, containing 2 cells per cubic millimeter and having a total protein content of 0.030 Gm. per hundred cubic centimeters. Tests for melanin in the spinal fluid and in the urine have given negative results. Roentgenograms of the skull show no evidence of destruction of the bone.

Comment.—The clinical picture in this case is what might result from any slowly growing midline tumor of the posterior fossa, and it proved to be only the nodular part of the tumor that caused symptoms, for its surgical removal afforded complete relief. The exceptional aspects of the tumor, aside from its microscopic appearance, were the nature of its spread and its seeming benignity. It appeared in the gross to be principally a tumor of the dura mater, although its microscopic aspects indicated that it probably had arisen from the arachnoid. Unfortunately, the relation of the arachnoid was not carefully ascertained at the time of operation, and, of course, the limits of the entire lesion were not in view; but even granting that the point of origin was the leptomeninges, as has been true in all of the previously reported cases, the remarkable thing is that the tumor should not have spread along the subarachnoid space, discoloring the pia and invading the parenchyma of the brain and the cranial nerves. That the pia was not widely involved is assumed from the fact that the surfaces of the cerebellar hemispheres and the exposed portions of the medulla were not visibly pigmented; yet the dura

on the left side was inky black, as could be seen in all directions. This then is more nearly comparable in the nature of its growth to extensive nodular invasion of the dura by meningiomas, sometimes spoken of as meningiomatosis. The unilaterality of such tumors has frequently been emphasized, though not accounted for; in our case the sharp line of pigmentation along the line of the occipital sinus was striking.

A further similarity of this tumor to the meningiomas was invasion of the adjacent bone, a frequent occurrence in the latter but heretofore unreported with the former. Grossly the pigment appeared limited to the cancellous portion of the bone, and there was no evidence of change in the general bony structure, though microscopic examination showed that all layers were pigmented. A review of the roentgenograms of the skull before operation and of others taken at intervals since fails to show definite abnormality of the bone.

The arrangement and morphologic character of the cells of this tumor are even more strikingly similar to those of the meningiomas than in the first case. But it must be granted that it is not possible to carry the comparison of all aspects of the tumor too far, since after all we do not have the advantage of a complete postmortem study, such as was made in all other reported cases of melanotic tumors of the meninges. Perhaps the most impressive aspect of the case is the complete absence of any indication of disease of the nervous system eighteen months after operation, which means that the remaining tumor, for a melanoma, has unheard-of benignity. Though some melanomas are said to be sensitive to roentgen irradiation and this form of therapy was employed, one cannot feel enthusiastic about its actual beneficial effect on so widespread a tumor.

GENERAL COMMENT

A large part of the literature dealing with melanomas is concerned with the problems of nosology, embryology and histiogenesis. It is unnecessary here to cite all the literature on the subject, and only the more recent developments of knowledge of these tumors need be mentioned. That melanomas are nervous in origin and possibly related to neurofibromas was suggested forty years ago by Soldan,[7] but the suggestion received little attention. There was widespread belief in their epidermal origin until Masson,[8] in 1926, convincingly established the nervous origin of dermal melanomas and demonstrated their derivation from specialized cells in the sensory nerve endings of the type of the

7. Soldan: Ueber die Beziehungen der Pigmentmäler zur Neurofibromatose, Arch. f. klin. Chir. **59**:261, 1899.

8. Masson, P.: Les naevi pigmentaires; tumeurs nerveuses, Ann. d'anat. path. **3**:417 and 657, 1926.

Wagner-Meissner corpuscles. Strong support for this idea has been lent by Ewing [9] and others.

A difficulty seemed to arise when it came to accounting in like manner for melanomas originating in the meninges. Foot and Zeeke,[10] however, pointed out the presence of many meningeal nerves that end in organs similar to the Wagner-Meissner corpuscles and, by the use of special staining methods, were able to demonstrate nerve fibrils in 2 melanomas which were primary in the meninges.

The other cells concerned in the formation of melanomas, besides the "nerve nevus cells," are pigment-bearing cells, sometimes called melanophores, chromatophores or melanoblasts, which, according to Ewing's strong contention, are themselves of nervous origin. It seems likely that the melanophore or chromatophore is of histiocytic origin, while the melanoblast is ectodermal and nervous in its origin. These pigmented cells are found normally in the leptomeninges of man, particularly at the base of the brain and in the recesses of the sulci and the fissures of the brain and cord. Their histogenesis as well as that of the leptomeninges is a highly contentious subject beyond the scope of this paper.

All of the primary melanomas of the meninges that have been encountered heretofore and reported, 1 or 2 at a time by a succession of authors, have been outstandingly malignant; in fact, all reports have been of postmortem observations. That all of the tumors have been eminently alike in most respects has contributed an aspect of finality about the nature and habits of the tumors. Primary melanomas elsewhere in the body, particularly those in the skin, are also malignant, but many are only potentially so and lie dormant for years. It is strange that less malignant melanotic tumors of the meninges have not come to light before this.

It may be that the tumors in our 2 cases were nothing more than quiescent melanomas; even so, they present many interesting findings and stimulate speculation along several lines. The points of gross resemblance to meningiomas and perhaps to lemmomas have been commented on and a striking histopathologic resemblance alluded to. Both tumors bore likeness microscopically to meningiomas in respect to the arrangement and the morphologic character of their cells; in addition, one of them showed areas resembling those seen in lemmomas (neurofibromas) and known as "Verocay bodies." While the whorls and bundles of cells might be interpreted as constituting the "lâmes foliaceées" of melanomas, they differ from these in two respects: their

9. Ewing, J.: The Problems of Melanoma, Brit. M. J. **2**:852, 1930.

10. Foot, N. C., and Zeeke, P.: Two Cases of Melanoma of Meninges with Autopsy, Am. J. Path. **7**:605, 1931.

morphology was more like that of the Verocay body, and no nerve fibrils were demonstrable anywhere in either tumor. Nerve bundles and fibrils are seen in the less malignant or nonmalignant melanomas almost invariably; in the malignant forms they may be absent. At first it was thought that the prominent bright red nucleoli of the cells of the cranial tumor might rule out a meningeal origin, but as the tumor from the cord showed the typical nuclei of meningocytes—and meningiomas sometimes show prominent nucleoli—this is not considered important.

It may be said that the only resemblance between our two tumors and the melanomas lies in the presence of pigment in both. They differed in that they showed no nerve fibrils and no mitotic figures, which would almost certainly be present in melanomas showing this degree of differentiation from the Meissner's corpuscle or its meningeal analog. If these tumors are considered from the standpoint of the standards of differentiation of meningiomas, however, the principal point that would not fit into the scheme is the presence of pigment. Careful examination of a number of meningiomas will sometimes disclose a hint of pigmentation, with small yellowish brown masses here and there; the pigment can be dismissed as merely hemosiderin under the usual circumstances. In tumors like the 2 under discussion, Perl stains show hemosiderin to be absent.

The conclusion may be ventured, then, that the tumors in our cases more nearly represented pigmented meningiomas than true melanomas. The fact that both patients are alive and well, one four years and the other one and one-half years after operation, speaks against malignant melanoma. Generalized metastasis and death would be expected in both cases if the tumors were ordinary malignant melanomas. The importance of this conclusion is manifest; it introduces a hitherto undescribed type of meningioma, and it places the latter in closer relation with the neurogenous tumors and farther away from the fibrogenous tumors, to which meningiomas have been allocated by several authorities.

SUMMARY

Two cases of primary melanotic tumors of the meninges, 1 of spinal and 1 of cranial tumor, are described. The patients were operated on and are living and well respectively four years and one and one-half years later. Except for the pigmentation the tumors were unlike the usual malignant melanomas of the meninges in every respect. Clinicopathologically and morphologically they resembled the meningiomas. We have suggested, therefore, that they were more nearly pigmented meningiomas. Even if it is granted that there may be minor discrepancies in our analogies, it can at least be concluded that these tumors are a link between the melanomas, the meningiomas and perhaps the lemmomas.

CYSTOMETRIC STUDIES IN CASES OF NEUROLOGIC DISEASE

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Objective study of bladder function in cases of neurologic disease is certain to add to knowledge of the anatomy and physiology of the neurologic control of the bladder. Suitable apparatus for recording bladder pressure graphically is necessary for study of bladder function. In a previous paper [1] we described a cystometer that combines the sensitivity of a water manometer with a continuous permanent record of bladder pressure. Later [2] we described an electrocystometrograph that eliminated the Harvard kymograph, smoked paper and breakable glass float of the first instrument. The latter instrument, although very sensitive to slight changes in pressure, is compact, durable and easily carried in the hand. These instruments have made it possible to study bladder function in a variety of patients with neurologic lesions and to have permanent records of their bladder function at various times.

ANATOMIC CONSIDERATIONS

The anatomy of the nerve supply of the bladder is worth reviewing. The bladder and its sphincters receive nerve fibers as follows (fig. 1):

Motor.—1. Somatic, arising from the third and fourth sacral segments and passing in the pudendal nerves to the external sphincter.

2. Parasympathetic nerves in the pelvic nerves, or nervi erigentes, arising from the second, third and fourth sacral segments and passing in these sacral nerves directly to the mural ganglia of the bladder wall.

3. Sympathetic autonomic nerves in the presacral or hypogastric nerve, arising from the first and second lumbar, and possibly the lower thoracic segments, and running in the presacral nerve to the hypogastric ganglia at the base of the bladder.

Sensory.—1. Afferent nerve fibers distributed through the pelvic nerves and originating from the dorsal root ganglia of the second, third and fourth sacral nerves.

From the Departments of Neurosurgery and Urology, Loyola University Medical School, and the clinics of Loyola University and Mercy Hospital.

1. Landes, H. E., and Voris, H. C.: A New Cystometer, J. Urol. **39**:813-816, 1938.

2. Landes, H. E., and Voris, H. C.: An Electrocystometrograph: Report of a New Instrument, J. Urol. **43**:345-355, 1940.

2. Afferent nerve fibers distributed through the presacral nerve and originating from the dorsal root ganglia of the midthoracic nerves, probably as high as the fifth or sixth thoracic segment. In this connection, both Learmonth [3] and we have produced subjective sensations in the bladder after stimulation of the central end of the divided presacral nerve in patients under spinal anesthesia. In Learmonth's patient the level of cutaneous anesthesia was at the tenth dorsal segment, in ours, at the eighth. Learmonth's patient complained of a "crushing" pain in the bladder; our patient complained that his bladder felt full.

Recently, when a cystometrogram was obtained of a patient with a complete transverse lesion (metastatic carcinoma) of the thoracic

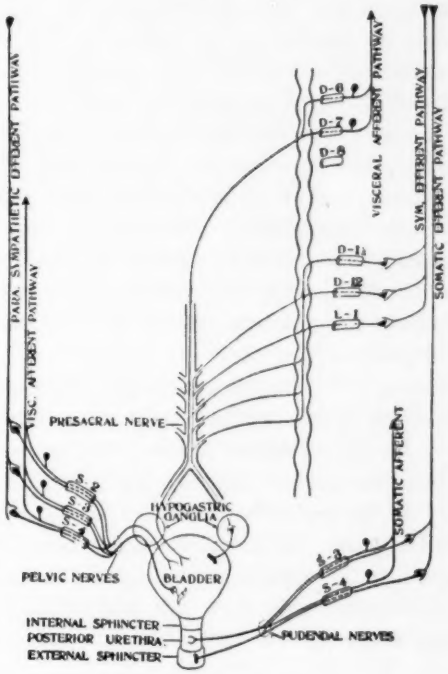

Fig. 1.—Diagram of bladder innervation as modified from Learmonth (Proc. Staff Meet., Mayo Clin. **6**:183, 1931).

region of the cord, with a cutaneous level at the sixth dorsal dermatome and complete loss of sensation (including deep pressure, pain and joint vibration sense) in the lower extremities, the patient complained of a sensation of fulness in his bladder and a desire to void after 150 cc. of filling. The desire to void ordinarily occurs in normal persons with about 150 cc. of filling. One of us (H. E. L.) has repeatedly observed in operating on the bladder of patients under spinal anesthesia (with

3. Learmonth, J. R.: A Contribution to the Neurophysiology of the Urinary Bladder in Man, Brain **54**:147-176, 1931.

the level of cutaneous anesthesia at about the tenth dorsal segment) that the patients did not complain if the bladder was cut or fulgurated, but did complain if the bladder was overdistended. We have repeatedly relieved intractable bladder pain by presacral neurectomy. This group of cases will be made the subject of a separate report in the near future, but observations on the patients make it certain that a considerable proportion of afferent impulses from the bladder are carried by sensory fibers contained in the presacral nerve.

The usually accepted concept of the sympathetic and parasympathetic innervation of the bladder has been that the former were the "filling" and the latter the "emptying" nerves of the bladder. Learmonth demonstrated in man that stimulation of the central end of the cut presacral nerve caused contraction of the internal sphincter, and he postulated that the sympathetic fibers, in addition to being motor to the internal sphincter, were inhibitory to the bladder wall. He also demonstrated rises in intravesical pressure in human beings with stimulation of the third and fourth sacral nerve roots, on one occasion, and of the second, third and fourth roots on another. There is no doubt that these segments contain the essential reflex mechanism for emptying the bladder. Resection of the presacral nerves in persons without disturbance of bladder function has little, if any, effect on micturition (occasional slight temporary frequency).

The exact role played by the sphincters in micturition remains to be determined, as methods of investigating their action have not been satisfactory. Simmons devised a method of obtaining isolated measurements of tone of both the internal and the external sphincter. He found the tone of the latter to be higher normally in both males and females, though less so in the latter. If it was lowered, especially if below that of the internal sphincter, the patient was usually incontinent. In bladders of the so-called hypertonic type, no matter what the origin, the tone of the internal sphincter was increased; in "hypotonic" bladders it was normal.

Denny-Brown and Robertson [4] studied bladder and sphincter function during micturition with an ingenious and elaborate apparatus and concluded that the internal sphincter contracts and relaxes in reciprocal relationship with the detrusor muscle of the wall of the bladder. They concluded that this is not at all under voluntary control; the only voluntary control is secondary to the effect of impulses from the cerebrum on the detrusor muscle. The external sphincter opens only after opening of the internal sphincter and closes spontaneously at the end of micturition before the internal sphincter. It can be closed power-

4. Denny-Brown, D., and Robertson, E. G.: On the Physiology of Micturition, Brain **56**:149-190, 1933.

fully in response to the effect of the will, but according to Denny-Brown and Robertson cannot be voluntarily relaxed. However, it is common urologic knowledge that it can be thus relaxed—witness the method of filling the bladder for irrigation by use of a small nozzle that just enters the external urethral meatus. However, we agree with the concept of Denny-Brown and Robertson that normal micturition is entirely secondary to active contraction of the bladder, and that voluntary micturition is effected solely by variation in conscious and unconscious inhibition of the mechanisms of spontaneous reaction to distention.

Our instrument gives an excellent and accurate picture of the activity of the detrusor muscle and reveals the point where the sphincters relax, that is, where active voiding about the catheter occurs. Slight leakage of a few drops of urine about the catheter reveals the forcing of the sphincter by a powerful detrusor muscle.

OBSERVATIONS

Normal Subjects.—Continuous records made during the filling of the bladder in persons with normal micturition and without urinary or neurologic complaints show that when fluid is introduced into the bladder through one channel of a two way catheter, the other of which is connected directly with the manometer, no significant rises in pressure occur until from 350 to 500 cc. of fluid has been introduced. This is due to the inhibiting influence of impulses from cerebral centers on the centers in the sacral portion of the cord (fig. 2). It must be explained that when the fluid is introduced into the bladder through a one way catheter which is also in communication through a Y tube with the manometer, with the introduction of each 50 cc. of fluid there is a prompt but unsustained rise in the manometric pressure (fig. 3). This rise is usually divided into two or more peaks. As can be readily demonstrated experimentally, its extent and duration vary with two factors: (1) inversely as the size of the catheter used, and (2) directly as the rate of injection. The rise is due to the greater resistance of the small bore catheter as compared with that of the manometer and its connections.

Ordinarily, subjective sensations are absent until about 150 cc. of fluid has been injected, when the subject usually recognizes a sensation of fulness of the bladder. A definite desire to void usually occurs at about 250 cc. of filling. Between 350 and 500 cc. of filling and either coincident with or shortly thereafter an injection, a powerful and sustained rise in intravesical pressure occurs. This is due to contraction of the detrusor muscle. The rise is sometimes slow, but is usually rapid. It lasts ordinarily from two to three minutes, and then a gradual fall in

pressure occurs, usually to near the base line. At or after the maximum pressure has been reached, voiding about the catheter often occurs. This may serve to inhibit further contractions of the bladder, or they may be repeated. Voiding about the catheter may not occur with the first contraction, but may be reserved for a later one. Occasionally, a series of prolonged painful contractions may occur without voiding about the catheter. Usually contractions of the bladder are attended with more

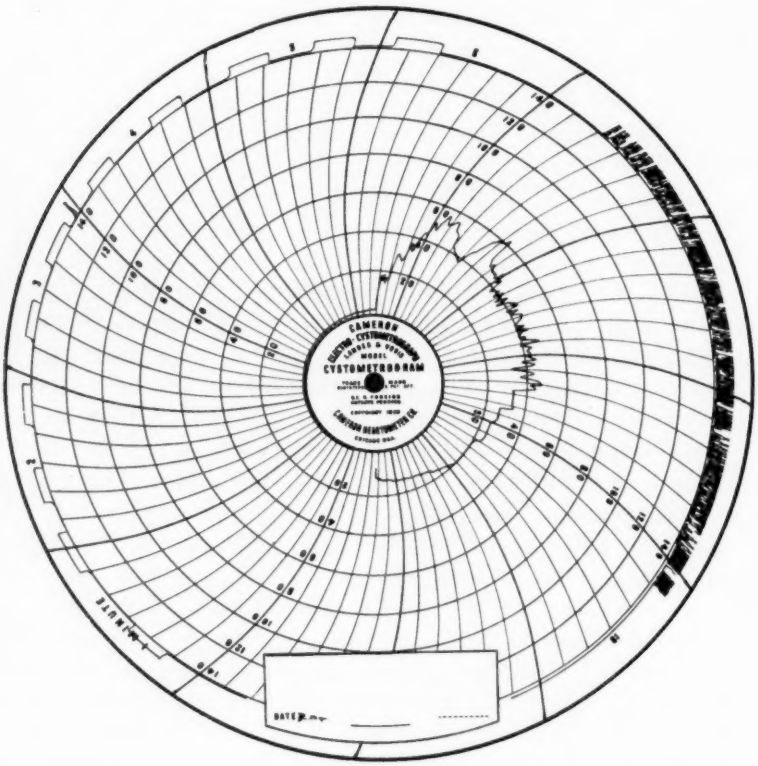

Fig. 2.—Cystometrogram of a patient with no evidence of neurologic or urologic disease. The tracing was made on the electrocystometrograph, with a two way 20 F. catheter in the bladder, and a total of 550 cc. of fluid was injected. As in all tracings made on the electrocystometrograph, the period of injection of each 50 cc. of fluid, the desire to void (when present) and the period of voiding are indicated on the margin of the tracing. Each radial line denotes a period of ten seconds. The concentric circles indicate pressure expressed in millimeters of mercury. It will be noted that there was practically no rise in bladder pressure until a bladder contraction occurred. This was after the introduction of 550 cc. of fluid and was later than the average for the normal subject, probably because of subconscious inhibition of bladder contraction on the part of the patient. The contraction lasted about five minutes, with a maximum intravesical pressure of 60 mm. of mercury and voiding for almost three minutes.

or less discomfort, but the converse is not true, as great discomfort may be present without any increase in bladder pressure. It seems certain that this discomfort is due to stretch of the bladder wall and not to any increase in intravesical pressure.

Lesions of the Upper and Lower Motor Neurons.—It early occurred to us that, theoretically, one might postulate neurologic disturbances in the function of the detrusor muscle of the bladder analogous to neurologic

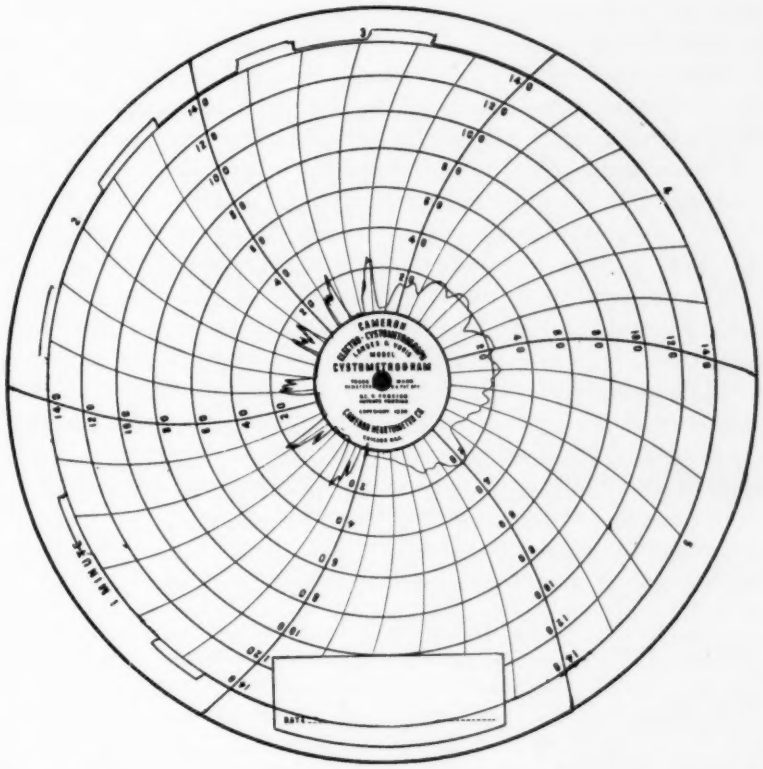

Fig. 3.—Cystometrogram of a patient with no evidence of neurologic or urologic disease. The tracing was made on the electrocystometrograph with a one way 18 F. catheter in the bladder, and a total of 300 cc. of fluid was injected. Note the prompt, but unsustained, rise in manometric pressure with each injection of 50 cc. of fluid. Voiding at the height of the bladder contraction did not occur in this patient. The contraction lasted for about two and one-half minutes, but only slightly exceeded a pressure of 20 mm. of mercury.

disturbances in that of striated muscle. That is, one might expect to differentiate an "upper" and a "lower" neuron type of vesical disturbance, just as there are upper and lower motor neuron syndromes of voluntary muscles. However, the lower motor parasympathetic neuron has its cell body in the hypogastric ganglia in the wall of the bladder itself. While

the hypogastric ganglia have been removed surgically in occasional instances, these cases have not been suitable for study of function of the detrusor muscle. Clinically, complete destruction of these ganglia by pathologic lesions which do not likewise markedly involve the wall of the bladder is not likely to occur.

There is marked difference, as Denny-Brown and Robertson,[5] Langworthy and his associates[6] and others[7] have shown, in detrusor function in cases of lesions involving the preganglionic neuron and that in cases of lesions above that level, that is, lesions involving the second, third and fourth sacral roots or the corresponding segments of the conus and lesions of the spinal cord or pyramidal pathways above that level. Langworthy and Kolb[8] expressed the belief, based on animal experimentation, that there is a center in the midbrain for control of tone of the detrusor muscle, but this has not been verified for man. Unquestionably, the outstanding influence of the cerebrum on bladder function is the subconscious inhibition of contractions of the detrusor muscle until several hundred cubic centimeters of filling has been accomplished. The pathways subserving this function must be closely associated with the pyramidal tracts, as lesions of these tracts usually cause loss of this inhibitory action to a degree that depends on whether the lesions are bilateral or unilateral. Langworthy and Kolb postulated that when cortical control is released there is overaction of the tonus center for the bladder in the midbrain, but the most marked development of small hypertonic bladders of neurogenic origin that we have seen has been in cases of bilateral transverse lesions of the spinal cord.

With lesions of the spinal cord or cauda equina there are three types of disturbance of micturition, according to Denny-Brown: 1. In the

5. Denny-Brown, D., and Robertson, E. G.: The State of the Bladder and Its Sphincters in Complete Transverse Lesions of the Spinal Cord and Cauda Equina, Brain **56**:397-463, 1933.

6. Langworthy, O. R.: Disturbances of Micturition Associated with Disseminated Sclerosis, J. Nerv. & Ment. Dis. **88**:760-770, 1938. Langworthy, O. R., and Dees, J. E.: A Study of Bladder Disturbances in Spina Bifida, J. Urol. **35**:213-226, 1936. Langworthy, O. R., and Lewis, L. G.: Urgency and Frequency of Micturition in Neurological Disease, Bull. Johns Hopkins Hosp. **56**: 211-223, 1935. Langworthy, O. R.; Lewis, L. G., and Dees, J. E.: Behavior of the Human Bladder Freed from Cerebral Control, J. Urol. **36**:577-597, 1936.

7. Kennedy, F., and Wortis, S. B.: The Effects of Some Nervous System Lesions on Genito-Urinary Mechanisms, J. Urol. **36**:255-260, 1936. Lewis, L. G.; Langworthy, O. R., and Dees, J. E.: Bladder Abnormalities Due to Injury of Motor Pathways in the Nervous System, J. A. M. A. **105**:2126-2132 (Dec. 28) 1935. Munro, D.: "The Cord Bladder": Its Definition, Treatment and Prognosis When Associated with Spinal Cord Injuries, J. Urol. **36**:710-729, 1936.

8. Langworthy, O. R., and Kolb, L. C.: The Encephalic Control of Tone in the Musculature of the Urinary Bladder, Brain **56**:371-382, 1933; Demonstration of Encephalic Control of Micturition by Electrical Stimulation, Bull. Johns Hopkins Hosp. **56**:37-49, 1935.

acute stage of the lesion there is depression of function with an inactive detrusor muscle and a tonic internal sphincter. 2. With lesions of the sacral segments of the cord or of the sacral nerve roots there is development of incontinence with straining and later spontaneous intermittent micturition. 3. With lesions above the sacral segments of the cord, with isolated reflex activity of these segments, there is complete development of automatic micturition. This may be associated with the so-called mass reflex, but is not actually a part of it, as Holmes [9] and later Langworthy [10] have shown. When it follows the mass reflex it is due to the initiation of bladder contraction by the violent contractions of the abdominal wall. Denny-Brown and Langworthy have shown that to initiate directly reflex micturition in these cases it is necessary to stimulate areas innervated by the sacral segments.

After autonomic or automatic micturition has developed, it may be temporarily or permanently abolished either by systemic or genitourinary infection in the patient or by any process that diminishes the activity of the lower reflex centers.

Lesions of the Upper Neuron: One would expect from the foregoing observations that disturbances of micturition resulting from cerebral lesions would always be characterized by small bladders with reduced capacity and by early, precipitous emptying. However, Watts and Uhle [11] reported 11 cases in which cystometrograms were obtained of patients with verified tumors of the brain. In only 3 was the bladder of this type; in the other 8 it showed definite hypotonicity, which was marked in some instances. No relationship between the type or location of the tumor and the dysfunction of the bladder could be discovered. It is apparent from the literature that a great deal remains to be elucidated concerning the cortical influence on micturition.

The effect of a great many neurologic lesions is to destroy in whole or in part the pathways for inhibitory impulses from the cerebral centers to the sacral portion of the spinal cord, or to suppress directly the activities of the cerebral centers themselves. In the infant reflex emptying of the bladder occurs without any inhibitory control from higher centers. A cystometrogram of one infant (fig. 4) shows graphically that such is the case. With a relatively small amount of filling a bladder contraction and voiding occur. As the child is "taught toilet habits," that is, to inhibit bladder contractions for a considerable period

9. Holmes, G.: Observations on the Paralyzed Bladder, Brain **56**:383-396, 1933.

10. Langworthy, O. R.: A Curious Illustration of "Mass Reflex" and Involuntary Micturition Following Injury of the Spinal Cord, Bull. Johns Hopkins Hosp. **60**:337-345, 1937.

11. Watts, J. W., and Uhle, C. A. W.: Bladder Dysfunction in Cases of Brain Tumor, J. Urol. **34**:10-30, 1935.

after he is conscious of distention of the bladder, he first learns to inhibit the contractions by impulses arising from centers above the level of consciousness (awareness). This gives him waking control of his bladder. Later, impulses below the level of awareness take over this function and night control is accomplished. Bladder contractions are then inhibited during sleep past the point at which distention of the bladder produces sufficient afferent impulses to awaken the subject. Some children, because of poor training or congenital instability, are unable to accomplish this and suffer from enuresis. Cystometric studies on a number of such children (fig. 5) clearly show that they lack the

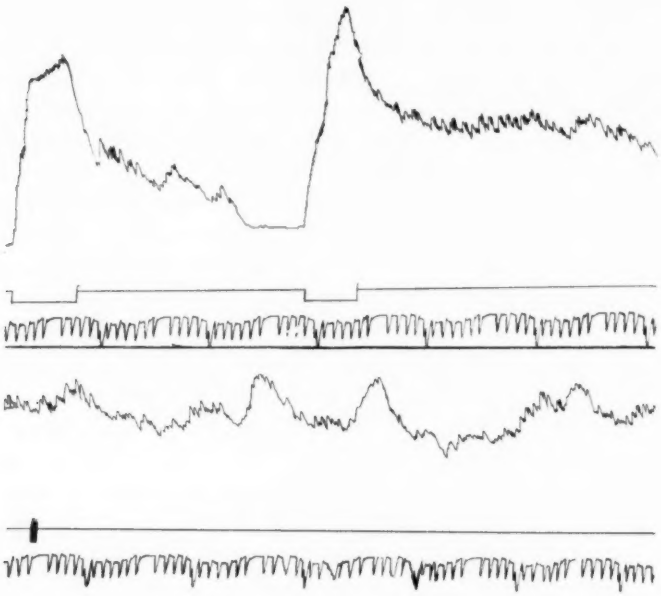

Fig. 4.—Cystometrogram of an infant of 18 months on whom no attempt to teach bladder control had been made. The tracing was made on a kymograph with a one way 10 F. catheter in the bladder. As in all tracings made on the kymograph, the time intervals are five seconds. The signal magnet shows periods of injection of 50 cc., the desire to void (when present) and voiding about the catheter. The tracing is in two sections, the lower being a continuation of the upper. A bladder contraction followed each injection of 50 cc., and voiding about the catheter occurred after the second injection. The child was crying during the procedure, and respiratory waves are larger than usual.

normal amount of inhibition of bladder contractions. These contractions occur abnormally early, and either simultaneous with or shortly after the first awareness of distention of the bladder. Many of these children, as might be expected, give a history of occasionally wetting themselves in the daytime if excited or in a position in which they

cannot readily relieve themselves. This further demonstrates the inadequacy of inhibition of reflex bladder contractions in these cases. This functional enuresis must be differentiated from disturbances due to organic lesions in the nerve pathways. This cannot always be done from the cystometrogram, so that studies of bladder pressure by no means eliminate the need for careful and detailed general and neurologic studies in all cases of bladder disturbance.

We have made cystometrograms of patients with various lesions of the brain and spinal cord involving the efferent motor pathways. As already pointed out, these patients should have bladders of reduced capacity with early contractions. In many cases this is true; in others, the reverse is true, and increased capacity with late contractions, or even none at all, is seen. In a case of tumor (meningioma) of the spinal cord at the level of the eighth dorsal segment the latter type of

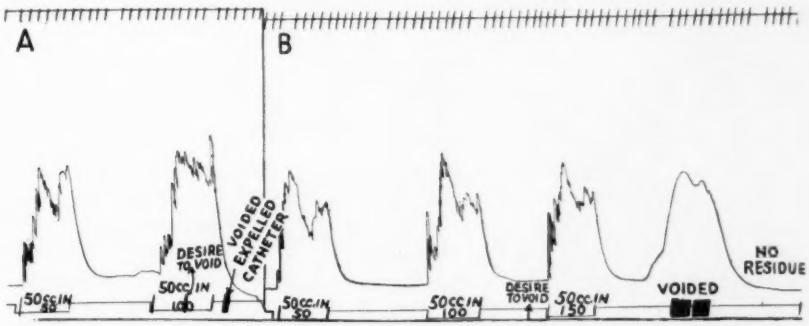

Fig. 5.—Cystometrograms of 2 boys, aged 8 and 13 years, with enuresis; one (*B*) had spina bifida occulta; neither had abnormal neurologic findings. The tracings were made on a kymograph with a one way 12 F. catheter in the bladder. In the first case desire to void and bladder contraction, with expulsion of the catheter, occurred with 100 cc. of filling. In the second case a desire to void was noted with 100 cc. of filling; a bladder contraction with voiding followed 150 cc. of filling.

tracing was shown (fig. 6). The patient had almost complete paralysis of the lower extremities. The same figure illustrates the tracing obtained a few weeks after operation. Function was rapidly returning, and the bladder had a contraction with voiding shortly after a desire to void was noted. This patient later, after complete neurologic recovery, had an entirely normal cystometrogram. Cystometrograms in 2 cases of advanced multiple sclerosis are shown in figure 7. The upper tracing shows no bladder contraction with 400 cc. of filling and a late desire to void (with 300 cc.). The lower tracing shows a bladder contraction with each 50 cc. of filling. It is of interest that after remission in the first case a bladder contraction and voiding were shown after 50 cc.

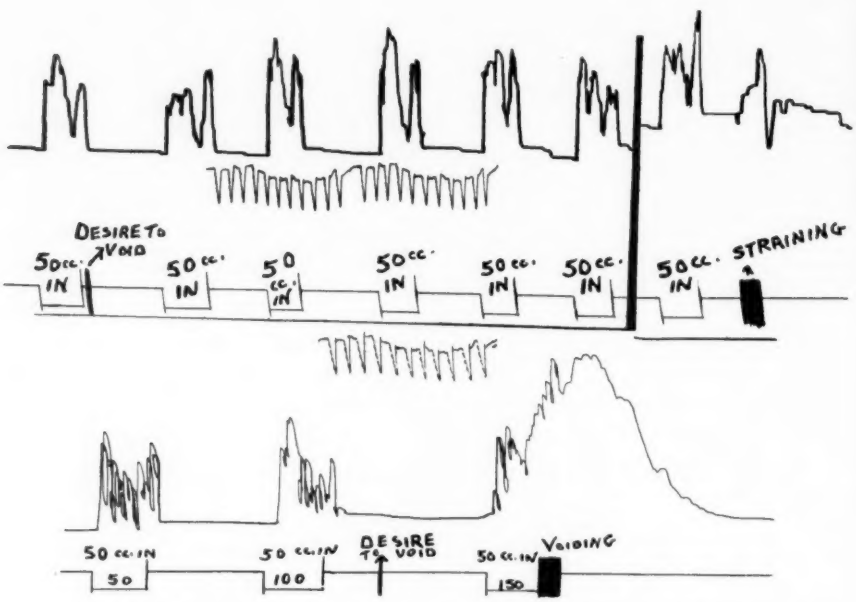

Fig. 6.—Cystometrograms of a patient with a tumor (meningioma) of the spinal cord at the eighth dorsal segment and almost complete paralysis of the lower extremities. Both tracings were made on a kymograph, using a 14 F. catheter in the bladder. The first tracing was made before operation. There was a desire to void after 50 cc. of filling, but no bladder contraction with 500 cc. of filling. A segment of tracing representing three minutes and 150 cc. of filling is omitted. The second tracing was made three weeks after operation. Function of the lower extremities was rapidly returning. A desire to void was noted with 100 cc. of filling and a bladder contraction with voiding with 150 cc. of filling.

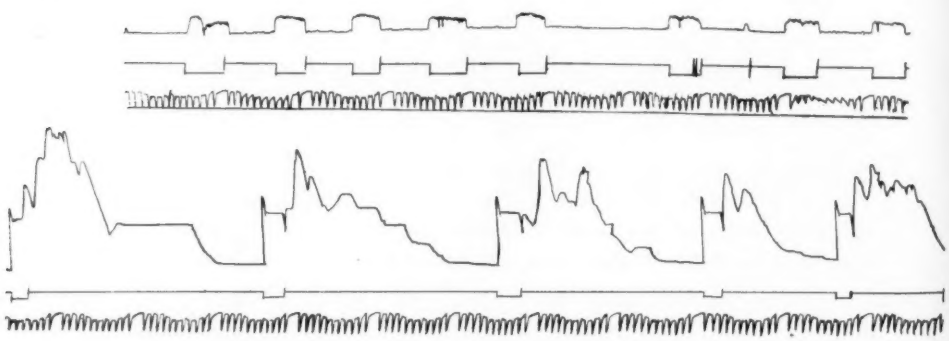

Fig. 7.—Cystometrograms of the patient with multiple sclerosis. Both tracings were made on a kymograph with a one way 16 F. catheter in the bladder. The upper tracing (first case) shows a late desire to void after 300 cc. and no bladder contraction after 400 cc. of filling. The lower tracing (second case) shows a bladder contraction with each 50 cc. of filling.

of filling (fig. 8). Similar conflicting observations have been made in cases of cerebral injury, tumor of the brain and cerebral arteriosclerosis. It is clear that diffuse lesions of the central nervous system above the level of the sacral region of the cord may result in radically different types of bladder dysfunction. This is difficult to explain until there is available more exact knowledge of the location of the efferent and afferent pathways related to bladder function, but we suspect it depends on the relative involvement of afferent and efferent pathways, and not on the particular level or type of the lesion.

The best examples of purely reflex bladders, comparable to the reflex bladder of the infant, have been seen in cases of complete transverse lesions of the cord. Figure 9 is a typical example of such an "automatic bladder." A bladder contraction with voiding appears with each 50 cc. of filling. This tracing was obtained from a boy aged 17 with Potts's disease and a complete transverse lesion of the cord, of two months' duration.

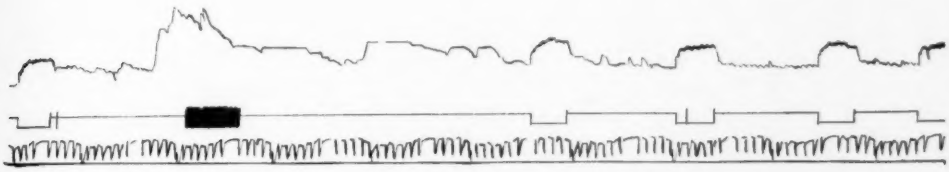

Fig. 8.—Cystometrogram in the first case shown in figure 7, made after a remission had taken place. The tracing was made on a kymograph with a 16 F. catheter in the bladder. After 50 cc. of filling a desire to void was noted, and then a bladder contraction with voiding occurred. After this, however, 200 cc. of fluid was introduced without any contraction, the initial reflex response having apparently been lost.

As is well known, the so-called automatic, or reflex, bladder does not appear at once after transverse lesions of the spinal cord in man, but usually requires weeks or months to develop. The general condition of the patient, freedom from urinary sepsis, trophic ulcers and such factors are of great importance in promoting its development. In our experience constant drainage of the bladder with an indwelling catheter, or, better still, use of Munro's [12] tidal drainage apparatus, greatly promotes the appearance of reflex contractions of the bladder. Cystometrograms at intervals enable the physician to have graphic records of the changing physiologic status of the bladder.

After such reflex activity of the bladder (automatic bladder) develops, the physician and patient are usually disappointed. Nursing

12. Munro, D.: The Treatment of the Urinary Bladder in Cases with Injury of the Spinal Cord, Am. J. Surg. **38**:120-136, 1937.

care is still complicated because of frequent involuntary voidings of small quantities of urine. In our opinion this is unavoidable. Reference to the normal cystometrogram shows a desire to void to be normally present with about 150 cc. of filling. In the infant or the child with faulty cerebral inhibition of bladder contraction (enuresis) there is a spontaneous bladder contraction simultaneous with or shortly after the first desire to void (in our cases, usually coincident with awareness of

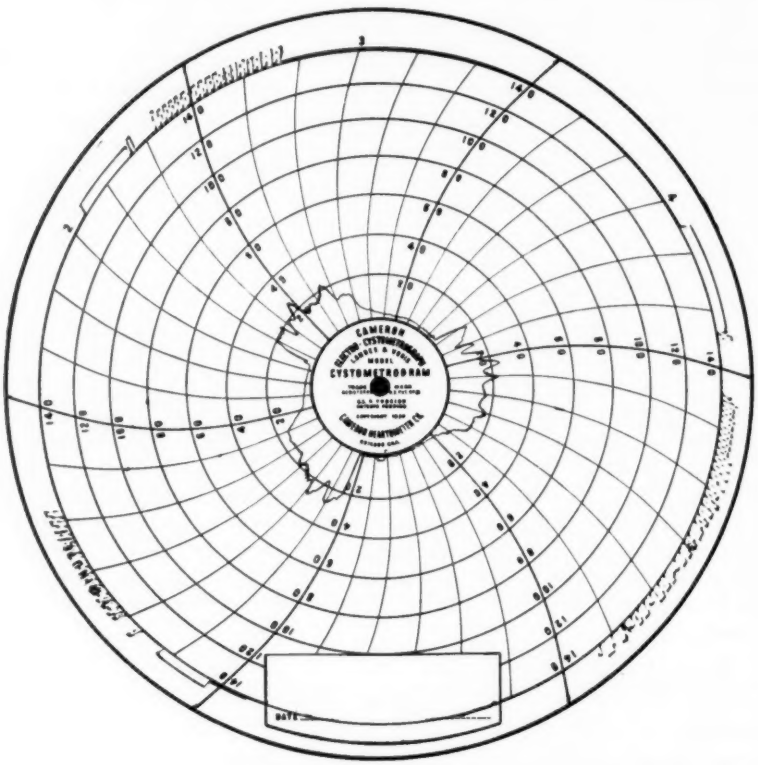

Fig. 9.—Cystometrogram of a 17 year old boy with a tuberculous epidural abscess of the spine and a transverse lesion of the cord at the level of the eighth dorsal segment, of two months' duration. The tracing was made on the electrocystometrograph with a one way 16 F. catheter in the bladder. There was a bladder contraction with voiding after each 50 cc. of filling.

bladder distention). It is to be expected in cases of complete transverse lesions of the spinal cord, with all efferent impulses from cerebral centers abolished, that a comparable situation will result and that therefore the maximum bladder capacity to be expected in these cases is in the neighborhood of 150 cc. Practically, it will usually be less because of the tendency of the bladder to become small and contracted with

constant drainage, and because of the frequency of at least mild degrees of cystitis and urethritis.

Cystometrograms made on patients under spinal anesthesia and on certain patients with acute complete transverse lesions of the spinal cord (figs. 10, 11 and 12) show certain unique characteristics. A desire to void or awareness of bladder distention may or may not be present, depending on the height of the level of the anesthesia or of the injury.

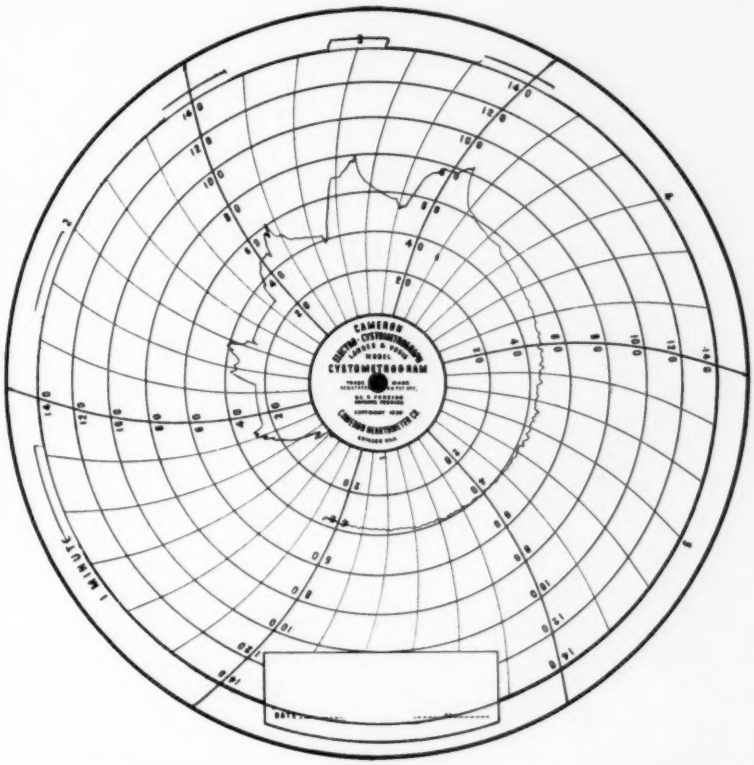

Fig. 10.—Cystometrograph of a patient under spinal anesthesia (sensory level at the seventh dorsal dermatome). The tracing was made on the electrocystometrograph with a one way 18 F. catheter in the bladder. Note the failure of the bladder pressure to return to the base line after each 50 cc. of filling and the steplike rise in the level of pressure following each injection of 50 cc. of fluid. After 250 cc. was injected, a high level of pressure was maintained at about 40 mm. of mercury.

After the initial injection (50 cc., usually) the pressure rises regardless of whether a one or a two way catheter is used and fails to return to the base line at completion of the injection. With each successive injection a higher peak is reached, and each new resting level is higher than

the previous one. Thus the record becomes a succession of steplike peaks and resting levels, each higher than its predecessor. What is the mechanism of production of such a record? We believe it is a "true" stretch reflex and represents a pathologic failure of the musculature of the bladder to accommodate itself to filling of the viscus. It must be a neuromuscular reflex depending on the activity of the postganglionic neuron in the bladder wall, unless the preganglionic neuron of the

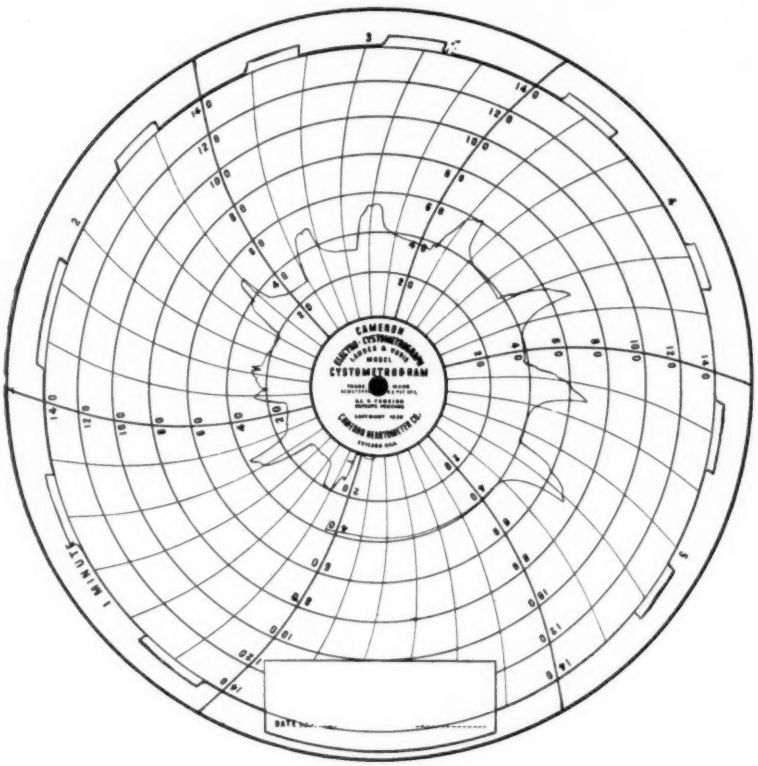

Fig. 11.—Cystometrogram of a patient with a recent acute transverse lesion of the spinal cord at the third dorsal segment, due to a bullet wound. The tracing was made on the electrocystometrograph with a one way 24 F. catheter in the bladder. There are failure of the bladder pressure to return to the base line after each increment of filling and a steplike rise in the level of pressure following each injection of fluid. A total of 500 cc. was injected, and after that a level of about 40 mm. of pressure was maintained. In spite of the high level of the lesion, the patient had a desire to void after 300 cc. of filling.

sympathetic system is involved in the mechanism of the reflex. The preganglionic parasympathetic neurons were interrupted in the case of the lesion of the cauda equina illustrated in figure 12; the upper motor

sympathetic and parasympathetic neurons in the case shown in figure 11, and in the other cases that we have studied.

We call attention especially to the high resting level of pressure maintained in these reflex bladders after the injection of several hundred cubic centimeters of fluid. In the 3 cases illustrated (figs. 10, 11 and 12) this level was about 40 mm. of mercury. Obviously, if the bladder is allowed to overdistend in a case of acute transverse lesion of the spinal cord or cauda equina, the kidneys are forced to work against

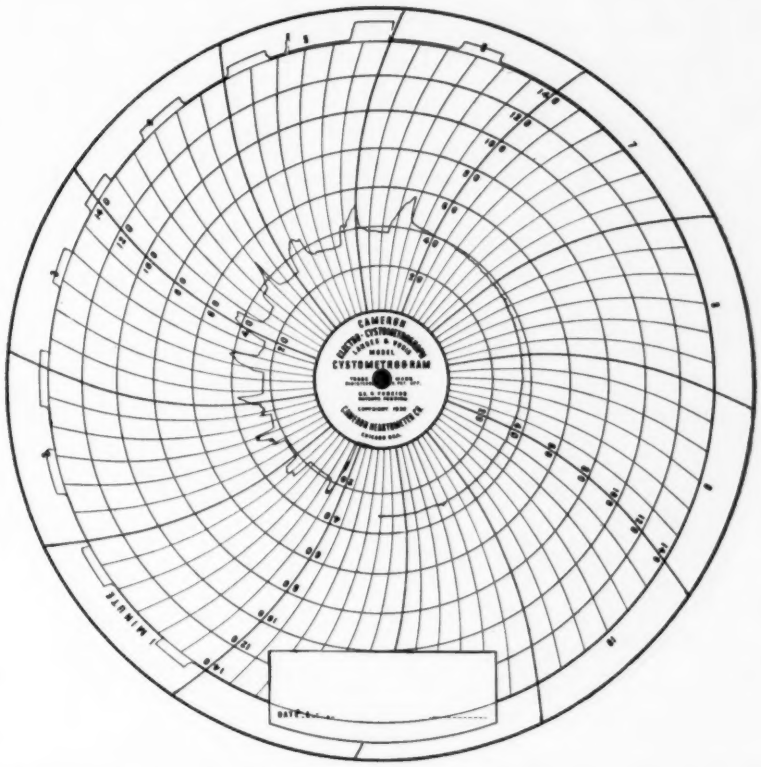

Fig. 12.—Cystometrograph of a patient with a recent acute transverse lesion of the conus medullaris and the cauda equina at the level of the first lumbar vertebra, due to a severe fracture dislocation. This lesion was verified by surgical exploration. The tracing was made on the electrocystomograph with a one way 22 F. catheter in the bladder. There are failure of the bladder pressure to return to the base line after each increment of filling and a steplike rise in the level of pressure following each injection of fluid. A desire to void was noted after 400 cc. of filling. A total of 500 cc. of fluid was introduced, and after that a high level of pressure was maintained at about 40 mm. of mercury.

a tremendous back pressure. This should be sufficient reason for instituting some form of bladder drainage immediately after an acute injury to the spinal cord or cauda equina.

This type of record differs from the persistently high resting level or basal pressure seen during filling of the bladder in cases of hypertrophy of the bladder musculature associated with obstructive lesions at the neck of the bladder (fig. 13). This resting level or basal pressure is established after the first injection, and then after each succeeding injection the pressure returns to this level (or is maintained there if a two way catheter is being used). This abnormal resting level of

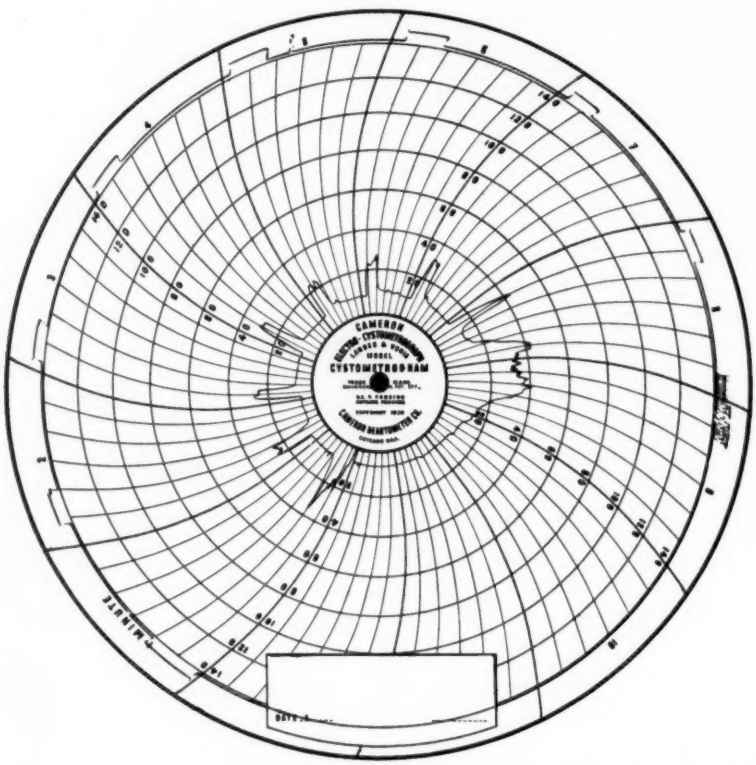

Fig. 13.—Cystometrograph of a patient with moderate hypertrophy of the bladder wall associated with partial obstruction, due to a benign adenoma of the prostate. The tracing was made on an electrocystometrograph with a one way 16 F. catheter in the bladder. There is failure of the bladder pressure to return to the base line after the first injection, but the new resting level thus established is maintained after each succeeding increment. There were a desire to void after 250 cc. of filling and a bladder contraction with voiding after 400 cc. of filling.

pressure seems to represent inability of the hypertrophied musculature of the bladder to accommodate itself completely to filling. It is usually about 10, and rarely as much as 20, mm. of mercury. Since the difficulty is purely muscular, the resting level that is maintained depends on the

degree of hypertrophy present and is not changed by successive increments of filling. In other words, the impairment of accommodation to filling that is due to hypertrophy of the bladder is effective to a certain level of pressure; above that level accommodation to filling is unaffected.

Lesions of the Lower Neuron: Lesions of the sacral portion of the spinal cord or of the cauda equina that involve the second, third and fourth sacral segments or the corresponding nerve roots involve the parasympathetic preganglionic motor neuron. Reflex activity of the

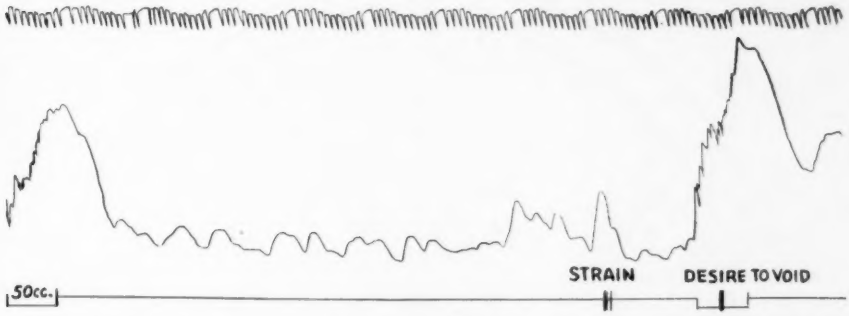

Fig. 14.—Cystometrogram of an 11 year old boy with normal lower extremities but incontinence dating from birth. There had been plastic repair of spina bifida in the lumbosacral region a few days after birth. The tracing was made on a kymograph with a one way 12 F. catheter in the bladder. There were a desire to void and a bladder contraction after injection of 100 cc. of fluid. Note the small, irregular, poorly sustained bladder contractions following the injection of 50 cc. of fluid.

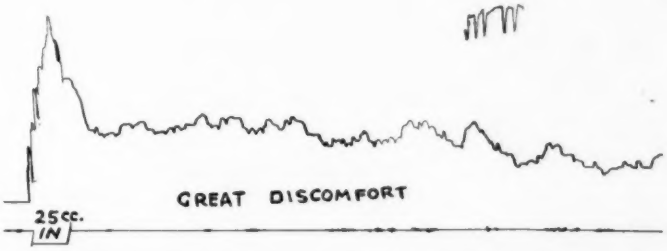

Fig. 15.—Cystometrogram of an 8 year old boy with congenital absence of the coccyx and the third, fourth and fifth sacral vertebrae. The lower extremities were normal, but there had been urinary and fecal incontinence since birth. The tracing was made on a kymograph with a one way 10 F. catheter in the bladder. The injection of 25 cc. of fluid caused great discomfort and a series of small, irregular, poorly sustained bladder contractions, on which were superimposed fluctuations of pressure due to exaggerated respiratory movements (crying).

bladder develops after the occurrence of such lesions (whether traumatic, inflammatory, neoplastic or congenital). When the lesions are complete, reflex activity is slower to develop than after transverse lesions (above the sacral level) of the spinal cord. The height of the pressure devel-

oped during contractions of the bladder is less with lesions of the cauda equina or the sacral portion of the cord than with lesions of the spinal cord above the sacral level. A marked characteristic of the cystometrograms in cases of chronic lesions of the cauda equina or the sacral portion of the spinal cord has been noted. It is the tendency of the bladder after partial filling to show a series of irregular, arrhythmic, poorly sustained contractions. We have not seen this in cases of any

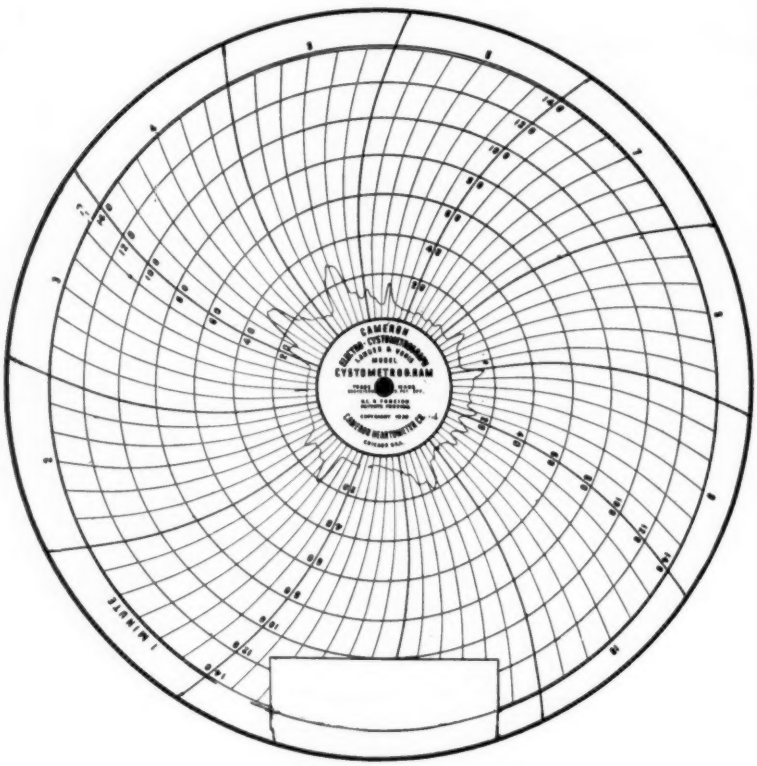

Fig. 16.—Cystometrogram of a patient who had suffered a fracture of the first lumbar vertebra fifteen years before. Paralysis of the lower extremities had been present at the onset, but complete recovery had taken place except for moderate atrophy of the calf muscles and occasional difficulty in starting the urinary stream. The tracing was made on the electrocystometrograph with a one way 18 F. catheter in the bladder. This tracing was made after the introduction of 125 cc. of fluid into the bladder. The small, irregular, poorly sustained bladder contractions characteristic of a chronic lesion of the cauda equina are well shown.

other type and have come to consider this phenomenon as diagnostic of such lesions. It is of value particularly in differentiating cases of enuresis of functional origin from cases of organic lesions of the cauda equina or conus medullaris (figs. 14, 15 and 16).

The Atonic Bladder.—There is a characteristic type of cystometrogram seen with a number of different neurologic lesions, inconstantly with many but constantly with at least one, viz., tabes dorsalis. This is the cystometrogram of the atonic bladder. Injection of as much as 1,000 cc. of fluid causes no rise in bladder pressure and no sign of bladder contraction. In some cases there is considerable discomfort, in others mere consciousness of bladder distention. Figure 17 is such

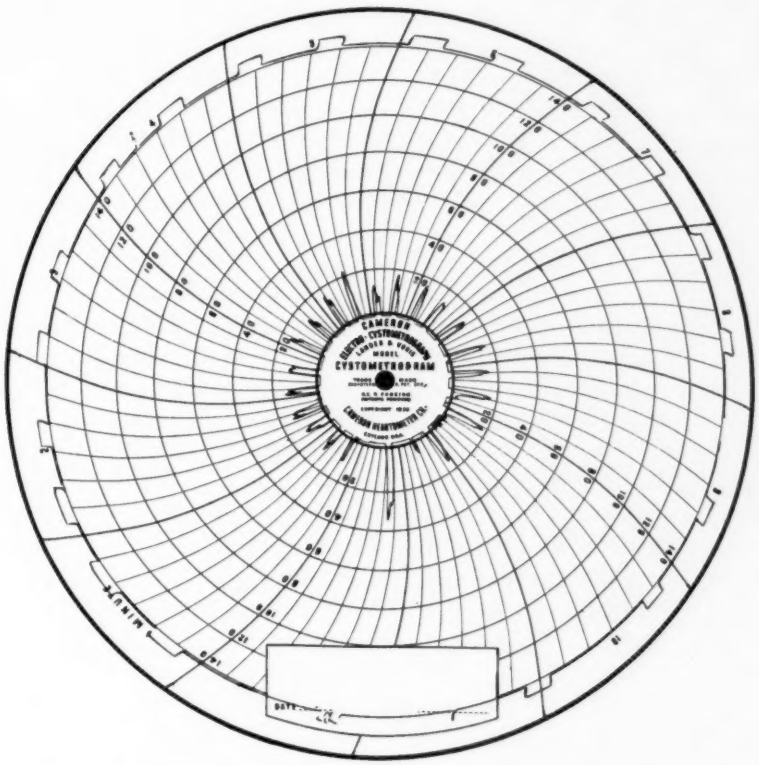

Fig. 17.—Cystometrogram of a 19 year old girl with dementia paralytica of tabetic type, the symptoms being of about eight months' duration. There were no subjective complaints referable to the bladder, but on direct questioning the patient admitted that voiding was infrequent and in large amounts. The tracing was made on the electrocystometrograph with a one way 16 F. catheter in the bladder. A total of 1,000 cc. of fluid was injected. A desire to void was noted after 350 cc. of filling, but no bladder contraction and no rise in the resting level of intravesical pressure was present with even 1,000 cc. of filling. During the final minute of the tracing no fluid was injected, but the effect on bladder pressure of, first, a cough and, second, voluntary straining are shown in the tracing.

a cystometrogram, made on a patient with dementia paralytica of tabetic type. In this case a desire to void was noted with 350 cc. of filling, but there was only moderate discomfort with even 1,000 cc. of filling.

In such a case as this the kidneys are not forced to work against back pressure developed by the bladder. Hence there does not seem to be any need for artificial drainage of the bladder in cases of this type, even if the bladder is chronically overdistended.

Obviously, in these cases there are loss of the normal emptying reflex of the bladder and marked impairment of sensation. In our opinion the loss of reflex contractions of the bladder is due in part (if not wholly) to reduction of afferent impulses from the bladder wall. There may be perhaps a certain group or type of afferent impulses from the bladder wall that are necessary to initiate reflex contractions. These are not necessarily impulses that reach the level of consciousness, for reflex contractions can and do occur when the sacral segments are cut off from higher levels. On the other hand, with acute lesions of the lower dorsal or lumbar regions of the cord, the patient may be conscious of distention of the bladder, but have no sign of bladder contractions.

Chronic overdistention may produce a bladder which clinically seems like that characteristic of tabes dorsalis. A woman with diabetes insipidus, of many years standing, had no neurologic symptoms pointing to any other involvement of the central nervous system. However, her cystometrogram showed a very late desire to void and no bladder contractions or rise in the resting level of bladder pressure with 1,000 cc. of filling. We believe that in this case chronic overdistention of the bladder was responsible for apparent reduction of afferent impulses from the bladder wall. The tendency to a late desire to void and late contractions of the bladder seen in the cystometrograms of many normal women may represent mild chronic overdistention associated with the habit of voiding at infrequent intervals.

SUMMARY

Objective study of bladder function in cases of neurologic disease adds greatly to an understanding of the various abnormalities of bladder function encountered. Such studies yield most information when made in the form of a continuous graphic record of bladder pressure during filling of the bladder.

In normal patients the desire to void usually occurs with from 100 to 300 cc. of filling, the average being about 150 cc. A bladder contraction usually occurs with between 300 and 500 cc. of filling, the average being about 350 to 400 cc. Voiding about the catheter may or may not be associated with the contraction.

Bladder contractions are essentially reflex, and the primary reflex center is in the second, third and fourth sacral segments of the spinal cord. Normally, they are inhibited until several hundred cubic centimeters of filling has been accomplished. In the infant a bladder con-

traction occurs with a relatively small amount of filling. This is also the case, but to a less marked degree, in cases of enuresis in children.

With complete chronic transverse lesions of the spinal cord an "automatic" or, better, reflex bladder is developed, which essentially functions in the same manner as the bladder of the infant.

Diffuse lesions of the central nervous system above the sacral portion of the spinal cord produce a variety of types of bladder dysfunction. Examples of such lesions are tumor of the cord and brain, injuries of the brain, multiple sclerosis and vascular accidents.

Cystometrograms of patients under spinal anesthesia or with acute transverse lesions of the spinal cord or cauda equina show a progressively higher peak of pressure with each injection and a progressively higher resting level after each injection. This is due to a neuromuscular reflex (stretch reflex) and depends on the activity of the postganglionic visceral motor neuron. A high resting level of pressure is maintained after filling in these cases. Patients with chronic lesions of the cauda equina show at some stage of filling small, irregular, poorly sustained bladder contractions.

In cases of tabes dorsalis and in some cases of chronic overdistention there is atonicity of the bladder wall with a late desire to void and absence of bladder contractions or any rise in bladder pressure even with 1,000 cc. or more of filling. There appears to be a marked reduction of afferent impulses from the bladder wall in these cases.

A constantly high resting level of pressure is seen in cases of hypertrophy of the bladder musculature due to obstructive lesions at the neck of the bladder. It is usually about 10 mm. of mercury and remains constant during filling. It depends on the degree of hypertrophy of the bladder musculature that is present and does not represent a neurologic lesion.

Case Reports

JACKSONIAN SEIZURES OF REFLEX ORIGIN

HANS STRAUSS, M.D., NEW YORK

Exact observations on epileptic seizures of reflex origin are extremely rare. No electroencephalographic studies in this field have been reported. The observations in the following case, besides presenting interesting clinical and electroencephalographic findings, furnish information on some central mechanisms and therapeutic possibilities.

REPORT OF A CASE

History.—A white woman aged 33 was admitted for special study to the New York State Psychiatric Institute and Hospital on Oct. 26, 1937, from Craig Colony, Sonyea, N. Y., to which she had been committed on July 24, 1929. The family history was irrelevant. There was nothing suggesting epileptic or epileptoid heredity. The facts in the personal history seemingly related to the condition under study were numerous. The patient was born after a normal pregnancy and delivery on June 1, 1904. She had pneumonia at the age of 15 months. When 18 months old she had a convulsion lasting several hours, during which she was unconscious. This convulsion was confined to the right side of the body, and for a few weeks afterward she had what she now calls "weakness of the right side." At 2½ years of age she had whooping cough, which was likewise associated with a convulsion, of about fifteen minutes' duration; there were no sequelae. In the last half of her eighth year she was knocked down by a car and struck on the back of her head. At this time she was not unconscious and had no convulsions, but complained of a headache for several days. About six months later the convulsive disorder became definite and continued without relief until the time of the present study. Since the onset she has had constant "weakness" and at times "running sensations in the right side of the body." Convulsive attacks have occurred at varying intervals since the onset. At Craig Colony seizures were noted as follows:

Year	No. of Grand Mal Attacks	No. of Petit Mal Attacks
1929	10	6
1930	8	28
1931	24	21
1932	23	32
1933	16	107
1934	17	25
1935	11	27
1936	12	37

From the Departments of Psychology and Psychiatry of the New York State Psychiatric Institute and Hospital.

This work was aided by grants from the John and Mary R. Markle Foundation and the Child Neurology Research (Friedsam Foundation) to Dr. Carney Landis and Dr. S. Eugene Barrera.

Read at a meeting of the New York Neurological Society, Oct. 4, 1938. An abstract and discussion of the paper appeared previously (Jacksonian Seizures of Reflex Origin: Report of a Case, Arch. Neurol. & Psychiat. **41**:423 [Feb.] 1939).

Status on Admission.—The patient complained of weakness and numbness in the right side of the body, associated at times with peculiar sensations, such as "a drop of water running down the arm." She herself differentiated her two types of convulsive disorders as "twitching" and "hard seizures," which she described as follows.

1. The "twitching" began first in the right eye, then spread to the right corner of the mouth and subsequently to the right arm and leg. At times it remained localized to the eye. Occasionally she was unable to swallow during these attacks, which lasted on an average from two to five minutes. The frequency of the attacks varied. Occasionally there were six attacks in one day, then there might be a week between any two attacks. She had not observed or registered the attacks carefully. She had noticed only that they started when she used the right arm. After the attack she felt increased numbness on the right side of the body for an hour. She associated two interesting episodes with this type of attack. Three or four years ago she hurt her right large toe in cutting the nail. This resulted in a painful local infection, of about two weeks' duration. During this period the twitching was frequent. About one and a half years ago she had an infected tooth on the right side. The twitching associated with this pain was particularly frequent.

2. The "hard seizures" began with a "warning" and a "funny sensation coming up the chest"; vision became dim, and the patient lost consciousness for about half an hour. Sometimes she could sit down between the warning and the attack, but at times she fell and hurt her head, usually at the back. She did not always fall to one side. Occasionally she bit her tongue during the seizure. These seizures also took place during sleep. The "hard seizures" occurred every two to four weeks, usually every four weeks, just before the menstrual period, at which time there might be two attacks in one day. In 1935 she had a condition of status epilepticus, fifteen attacks occurring during one night.

Examination.—The patient was slender and of asthenic body build. General examination, including various roentgenographic observations, disclosed no abnormalities of the inner organs. The general blood picture also was within normal limits. Neurologic examination revealed definite abnormalities. There was a constant slight contraction of the muscles around the right corner of the mouth. There was paralysis of the right leg, arm and hand, and the right hand felt colder than the left. The deep reflexes, including the knee jerk, ankle jerk, and biceps, and radial reflexes, were exaggerated on the right side. The gait showed spasticity on the right side. There were no abnormal reflexes on either side, except for a positive Babinski response on the right. Sensory abnormalities were limited to hemihypesthesia on the right, including the limbs, trunk, tongue and mucosa of the mouth on that side. This was true for touch, warmth, cold and taste. Hypalgesia was present over the same area. Diminution in sensory response was slightly less marked toward the midline, but showed no decrease in severity toward the proximal parts of the limbs. There was no disturbance in stereognosis or in the sense of position, vibration or smell. Hearing was normal and equal on the two sides. No hemianopic defect was found.

Roentgenographic examination of the skull revealed an irregular area of calcification, measuring about 1 by 2 cm., behind the motor area on the left side, about 1 cm. internal to the inner table. The calcified area was not sharply demarcated. An air encephalogram revealed enlargement of the left ventricle, with rounding of its lateral corner. Close to the calcified area, and between this area and the posterior portions of the frontal lobe, was a marked accumulation of air

on the surface of the brain, indicating a number of extremely wide, deep sulci (fig. 1). Studies of the cerebrospinal fluid revealed nothing abnormal.

Provocation of Jacksonian Seizures.—A. Effective Stimuli: In the early observations jacksonian seizures, limited to the right side, could be obtained by the following means: 1. Tactile stimuli: (*a*) Stimulation of the skin, e. g., rubbing the skin gently anywhere on the right half of the body, pricking with a needle or blowing air into the external auditory canal. Similar rubbing of symmetric points on the two sides of the body simultaneously produced the same effect as rubbing on the right side only. No attack was provoked by simply touching the patient or by stimulation with cold or warmth. (*b*) Stimulation of the mucous membranes on the right side, e. g., touching the cornea. (*c*) Stimulation of the skin and deeper structures simultaneously on the right side, e. g., elicitation of the knee or ankle jerk or percussion of the abdomen.

2. Gustatory and olfactory stimuli: These were ineffective. Smelling ammonia, however, which causes painful sensations in the nose, initiated twitching.

Fig. 1.—Pneumoencephalograms showing an area of calcification behind the left motor area and increased accumulation of air over the left hemisphere.

3. Visual stimuli: Results differed, depending on which eye and which part of the retina were stimulated. Diffuse illumination of the right eye produced a convulsive seizure with a shorter period of stimulation than did similar visual stimulation of the left eye. In addition, the convulsive symptoms were more severe with diffuse illumination of the right eye. Illumination of either eye by flashing a light produced, on the average, a greater convulsive effect when the light was projected to a point of the retina corresponding to the right visual field than when it was projected to a symmetric point corresponding to the left visual field. Table 1 demonstrates the much greater effect with stimulation of less duration of points in the left eye corresponding to the right visual field than of points in the left eye corresponding to the left visual field. On the average, when the light was flashed into one eye only, the convulsive effect was greater than when the same stimulus was presented simultaneously to the other eye. This is demonstrated in table 2. Exposure to daylight, sunlight or photoflood light, used in taking moving pictures, did not produce any attack.

4. Auditory stimuli: By means of ear phones connected with an oscillator, sounds of various frequencies were presented to each ear alternately. These tests revealed that stimulation of the right ear was much more effective than stimulation of the left ear. When the sound was presented to the left ear the duration of

stimulation had to be longer, and usually the effect was only a tonic contraction, without clonus. Shorter stimulation of the right ear produced a clonic response (table 3). During some of the tests the stimulating sound was interrupted as soon as any convulsive symptoms appeared. When this was done the response

TABLE 1.—*Effect of Stimulation of Left and Right Visual Fields of the Left Eye*

Left Eye			
Left Visual Field		Right Visual Field	
Duration of Stimulation, Sec.	Effect	Duration of Stimulation, Sec.	Effect
>30	0	15	Clonus
15	Clonus	13	Severe clonus
39	Very slight clonus	15	Severe clonus
>32	0	10	Very severe clonus

TABLE 2.—*Difference in Effect of Stimulation of One Eye and of Both Eyes*

Right Eye		Both Eyes	
Duration of Stimulation, Sec.	Effect	Duration of Stimulation, Sec.	Effect
10	Clonus		
11	Clonus		
		43	Very slight clonus
		23	Clonus
8	Clonus		
19	Swallowing		
		35	Swallowing
17	Severe clonus		
		24	Clonus

TABLE 3.—*Difference in Effects of Stimulation of the Right and the Left Ear*

Left Ear		Right Ear	
Duration of Stimulation, Sec.	Effect	Duration of Stimulation, Sec.	Effect
>60	..		
		15	Clonus
		13	Clonus
50	Tonus		
30	Tonus		
		15	Clonus
35	Clonus		
		13	Severe clonus
		15	Very severe clonus
30	Tonus		
		13	Very severe clonus
		15	Severe clonus
40	Clonus		

remained confined to the right half of the face and to the neck. In other tests, even though convulsive manifestations occurred, the sound presented to the right ear was continued. When this was done the clonus spread to include finally the whole right half of the body, involving successively the neck, the arm and the leg. Finally, even though the stimulation was continued the attack stopped. New convulsive manifestations reappeared, however, if the frequency of the sound was changed without interrupting the stimulation. When the same sound was presented simultaneously to the two ears, the effect was essentially the same as when the sound was presented to the right ear only.

5. Vestibular stimuli: Stimulation by rotation or galvanization of the ear did not produce any convulsive phenomena. Injection of cold water into the right external auditory canal initiated slight twitching. This appeared immediately on injection of the water, before any vestibular symptoms could be observed, and stopped before the disappearance of the vestibular symptoms; this indicated that the twitching was probably the effect of sensory stimulation of the auditory canal, and not of the vestibule itself.

6. Movement stimuli: When various deep reflexes, including the knee jerk, ankle jerk and triceps and other tendon or periosteal reflexes, were elicited twitching occurred. Voluntary movements, including blowing up the cheeks and alternately raising and lowering the right foot, produced the convulsive manifestations. Numerous modifications occurred in these tests; e. g., when a movement which when actively performed provoked twitching was imitated passively, the attack did not occur. For example, voluntary performance of the finger to nose test on the right initiated twitching which did not occur when the finger was passively brought up to the nose by the examiner. Likewise, reproduction of a voluntary movement by electrical stimulation did not provoke the attack which was produced by voluntary movement itself. When a voluntary movement, which initiated convulsions when performed actively and in an isolated manner during the experiment, was performed as part of a general action of daily life, it did not produce any convulsive manifestations; e. g., walking did not initiate a twitching response, but isolated raising and lowering the right foot did. Again, chewing during meals did not initiate an attack, but chewing movements imitated on command did. When a voluntary isolated movement had been used for a long time to produce an attack it finally became ineffective. When this occurred it was observed that the patient performed the movement much more easily than at the beginning of the period of observation. It appeared that she had learned to perform the movement without paying any special attention to its execution. When the same movements were performed symmetrically on the two sides of the body, the effect was the same as when the right side only was used. Turning the head to the right was more effective than turning it to the left. Optokinetic nystagmus was most effective when the fast movement was directed toward the right side or downward. Finally, psychic activity alone did not initiate twitching, as was proved during the course of many psychologic tests.

B. Form of Convulsions: During the preceding tests the form of convulsive manifestations remained constant, affecting the right side only. The minimum manifestation of abnormal innervation was seen as a tonic contraction, usually around the right corner of the mouth and sometimes extending around the right eye. A somewhat more widespread response consisted of similar twitching with convulsive swallowing movements, due to involuntary contractions of the right supralaryngeal muscles and associated with contraction of the platysma. The more severe attacks elicited by these tests started either in the stimulated limb or in the face, after which they spread over the whole right side of the body, involving first the portions of the body adjacent to that initially responding and manifested by general unilateral clonic convulsions, or occasionally by clonic convulsive movements of the face and arm with tonic contractions in the leg.

C. Further Observations: On Nov. 19, 1937, 2 drops of a 4 per cent solution of cocaine hydrochloride was instilled into each conjunctival sac. This served as a control for the experiments on stimulation with light by eliminating through anesthesia any possible stimulation of the cornea and conjunctiva. Three minutes after instillation, the corneal reflex was abolished on both sides simultaneously. It was impossible to initiate any attack by stimuli such as touching the cornea,

voluntary active movements of the right side or acoustic or optic stimuli. This refractoriness lasted for twenty-four hours, at the end of which twitching could again be elicited by various stimuli; these, however, had to be of greater intensity than before the instillation of cocaine. Likewise, the twitching response was not as marked as before. Subsequently, 1 drop of the solution of cocaine was instilled into the left conjunctival sac. No effect on the convulsive manifestations with various forms of stimulation occurred. However, application of the solution of cocaine to the right eye caused complete disappearance of the convulsive responses. It is of interest that subsequent to the initial application of cocaine to the eyes convulsive manifestations could not be reproduced with the same regularity and intensity as before. After application, more prolonged and more intense stimulation than was initially used elicited only relatively slight convulsive manifestations.

During one period, from Jan. 4 to Feb. 4, 1938, at which time an encephalographic examination was made, the administration of cocaine was stopped. Subsequent instillation of cocaine always abolished all convulsive symptoms for from one to two days. After this completely refractory period the convulsive excitability returned to some extent, never, however, reaching its initial degree. In short, the effects of cocaine seemed to be of two types: a temporary and a more permanent one. The temporary effect was that of the complete refractory period, lasting a day or two, and the permanent effect manifested itself as a constant decrease of excitability. During the periods of improvement there was some amelioration of the hemiparesis on the right side, especially in the leg, in which the muscular strength improved and approached that in the left, and the Babinski response disappeared. The effect of cocaine on the response to hyperventilation was interesting. Before administration of cocaine the movements and sensory stimulation associated with hyperventilation produced convulsions after a few seconds. The interval was too short for a biochemical effect of the hyperventilation. Subsequent to administration of cocaine, however, hyperventilation produced jacksonian seizures on the right side. At times, however, this effect could be reduced, and at times even completely suppressed, by the application of cocaine to the eye. In addition, movements of the limbs on the right which previous to administration of cocaine produced convulsive manifestations could be performed subsequent to the application of cocaine without convulsions. Cocaine was effective in the manner described only when it was applied to the right conjunctival sac. Application to the left eye, to the nasal mucosa and to the pharynx, or subcutaneous injection did not produce the same effect.

D. Spontaneous Convulsive Symptoms: As stated earlier, the patient also suffered from spontaneous seizures. Some of them appeared during sleep. These seizures were of jacksonian type and occurred on the right side. Cocaine also favorably influenced these seizures. In addition to the applications of cocaine, the patient received phenobarbital, which she had taken for many years. Continuous administration of phenobarbital, even in doses of 4½ grains (0.263 Gm.) a day, had failed to diminish either the reflex convulsive manifestations or the spontaneous seizures.

Electroencephalographic Studies.—For these studies two amplifier systems, operating crystal ink-writing recorders, were used. By the use of two channels the records were taken simultaneously from bilaterally symmetric points on the skull. When the records were observed simultaneously on the two sides, that on the left being recorded from above the area of calcification and that on the right from a symmetric point, the following characteristics could be observed (fig. 2): 1. The per cent time alpha on the right was 30 and that on the left 10. 2. The alpha rhythms on the right were fairly well defined and appeared in large groups, whereas those on the left occurred only in groups of 2 or 3, and were modified by

other frequencies. 3. The alpha frequency (9 per second) was the same in the two hemispheres. 4. Potentials of low frequency, of about 3 to 6 per second, appeared more often in the record from the left side. 5. When the total electrical activity was obtained, the difference between the actual measurement of the brain wave

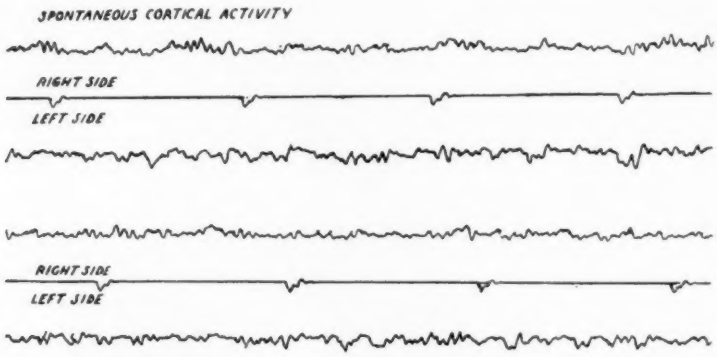

Fig. 2.—Electroencephalographic records taken simultaneously from bilaterally symmetric points on the skull.

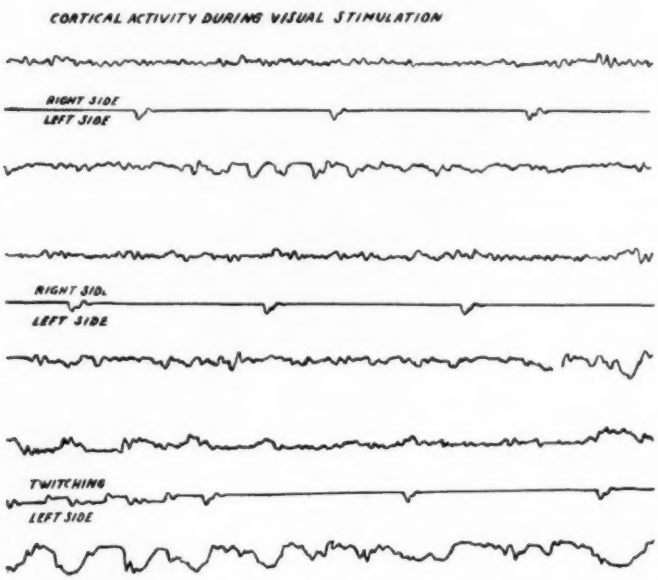

Fig. 3.—Electroencephalographic records showing effect of stimulation of the right eye with light.

record and the length of the tape for sixty seconds was 121 cm. on the left side and 77 cm. on the right.

Application of cocaine to the right eye did not influence the spontaneous electrical activity of the brain. Flashing light into the right eye, however, was associated with changes in the electroencephalogram (fig. 3). Three per second waves of high

potential appeared, associated with twitching around the right corner of the mouth. The slow waves did not appear when the same stimulus was applied after cocainization of the right eye. The potentials, without a doubt, were true brain potentials, because they could not be reproduced by having the patient imitate the twitching movements actively. Moreover, their appearance in the records from the left side makes it improbable that they represent muscle potentials from the muscles on the right side of the face.

COMMENT

The symptoms in this case were in all probability the manifestations of a lesion of the brain acquired in early childhood. It is probable that the lesion was caused by a hemorrhage or some form of encephalitis. The roentgen studies and air encephalograms also contributed to this diagnosis. The exact extent of the lesion could not be determined, but on the basis of the encephalogram and the clinical findings it is highly probable that the destructive process involved the left cortex between the posterior portions of the frontal lobe and the parietal lobe. There was no indication of any lesion of the optic radiation or of the corpus callosum.

Owing to the fact that peripheral stimuli, e. g., incidental hitting of the right side or movements of the intestine, may probably have been sufficient to produce an attack, it cannot be said with certainty to what extent the apparently spontaneous jacksonian seizures were really spontaneous or were merely masked reflex seizures.

The so-called reflex seizure could be induced by stimulation of one of many structures. Stimulation of the skin, subcutaneous structures and mucous membranes was effective only when performed on the right side. Additional cases of this type, in which cutaneous stimulation induced epileptic attacks when applied to a point in the periphery corresponding to a cerebral focal lesion, have been described by Critchley,[1] Holmes,[2] Pontano[3] and Rosenhain.[4] Reflex seizures in other cases in which pathologic lesions were more diffuse have been described by Wilson,[5] Longo,[6] de Marco[7] and Martino.[8] Critchley, in discussing the observations of Jackson[9] and Kennedy,[10] pointed out the importance of

1. Critchley, M.: Ueber Reflex-Epilepsie, Schweiz. Arch. f. Neurol. u. Psychiat. **35**:256, 1935.

2. Holmes, G.: Local Epilepsy, Lancet **1**:957, 1927.

3. Pontano, T.: Zone cutanee epilettogene ed epilessia riflessa, Policlinico (sez. med.) **30**:425, 1923.

4. Rosenhain, E.: Ueber Reflexepilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **64**:99, 1921.

5. Wilson, S. A. K., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 17, p. 1.

6. Longo, V.: Epilessia riflessa de eccitamenti afferenti nell'uomo, Riv. di pat. nerv. **45**:153, 1935.

7. de Marco, R.: Su un caso di epilessia umana riflessa, Riv. di pat. sper. **11**:350, 1933.

8. Martino, G.: Epilepsia experimentale e humana, An. Inst. nac. de parasitol. **5**:5, 1932.

9. Jackson, H.: On a Case of Fits Resembling Those Artificially Produced in Guinea Pigs, Proc. Med. Soc., London **10**:87, 1878-1885.

10. Kennedy, F.: The Symptomatology of Temporo-Sphenoidal Tumors, Arch. Int. Med. **8**:317 (Sept.) 1911.

surprise for the convulsant effect of stimuli. However, in the present case some definitely disagreeable character, rather than surprise, seemed to be a common factor in the effective stimuli.

Provocation of convulsive seizures by acoustic stimuli has been described repeatedly. Two cases in which the acoustic stimuli were similar to ours were those of Foerster [11] and Pick (cited by Higier [12]). In contrast to the fact that stimuli from the skin and mucous membranes were, in our case, effective only when applied to the right side of the body, acoustic stimuli were effective from either ear, although the convulsive symptoms were much more severe when the sound was presented to the right ear. This is explainable in light of the anatomic observation that the crossed auditory radiation is larger than the uncrossed. This observation, together with that obtained in regard to optic stimuli, indicates that sensory stimuli of this type were effective only insofar as they were directly conducted to the left hemisphere, the site of the pathologic lesion. It is difficult to state the exact characteristic in the acoustic stimuli responsible for the production of the convulsive symptoms. Unlike stimulation of the skin, there was no element of disagreeableness or surprise common to all the effective auditory stimuli.

Many of the effective auditory stimuli observed by other authors were different from those observed in our case. One need only compare our stimuli with the surprising noises or sounds causing the attacks of acoustic motor epilepsy and with the specific melodies in the cases of musicogenic epilepsy recently collected by Critchley.[13]

Optic stimuli as effective in provocation of convulsive seizures have been described by Catola,[14] Critchley,[1] Goodkind,[15] Holmes [2] and Radovici, Misirliou and Gluckman.[16] However, relatively incomplete analyses of these cases were presented. As mentioned, the greater effectiveness of stimuli to the left hemisphere was evident. Stimuli presented to the right visual field were thus much more effective than those presented to the left visual field. Whether the stimuli which produced the attacks when light was flashed to the parts of the retina corresponding to the left visual field were indeed stimuli coming from the left visual field cannot be definitely stated. It may be that in flashing light to the right half of the retina of one eye a certain amount of light also reached the left half and therefore produced a minor convulsant effect. The greater effectiveness of stimulation of the right eye is clear

11. Foerster, O.: Die Pathogenese des epileptischen Anfalls, Deutsche Ztschr. f. Nervenh. **94**:15, 1926.

12. Higier, H.: Auslösung und Coupierung von klonischen und tonischen Muskelkrämpfen durch periphere Eingriffe, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:730, 1928.

13. Critchley, M.: Musicogenic Epilepsy, Brain **60**:13, 1937.

14. Catola, G.: Epilessia sensoriale visiva provocata dai raggi solari, Riv. sper. di freniat. **58**:1191, 1935.

15. Goodkind, R.: Myoclonic and Epileptic Attacks Precipitated by Bright Light, Arch. Neurol. & Psychiat. **35**:868 (April) 1936.

16. Radovici, A.; Misirliou, V., and Gluckman, M.: Epilepsie réflexe provoquée par excitations optiques des rayons solaires, Rev. neurol. **1**:1305, 1932.

when one bears in mind that, according to Metzger [17] and Schaffer,[18] in either eye the nasal half of the retina predominates, and therefore the right visual field is better represented in the retina of the right eye than in that of the left eye. The greater effectiveness of stimuli coming from the eye opposite the affected hemisphere agrees with the experimental findings of Fulchignoni [19] that directly after strychninization of one occipital lobe convulsive seizures could be provoked best by visual stimulation of the contralateral eye. A satisfactory explanation of the fact that simultaneous illumination of both eyes was less effective than illumination of one eye alone is far from easy. With this type of stimulation the stages of excitation in the optic centers of the two hemispheres are probably well balanced and about equal, whereas with stimulation of one eye probably a greater difference exists between the stages of excitation in the optic centers of the two hemispheres. This might suggest that the higher degree of stimulation in the left hemisphere as compared with that in the right is a more important factor for the production of the attacks than the absolute degree of stimulation of the left hemisphere. However, such an explanation is not very probable because a corresponding relationship between unilateral and bilateral acoustic and tactile stimuli does not exist. It can be stated only that the convulsive effect of a stimulus may be reduced by the simultaneous application of another stimulus and that more stimulation does not necessarily mean a greater convulsive effect.

Stimuli of taste and smell and vestibular stimuli did not provoke attacks. No cases have been observed in which such stimuli were effective.

In most published cases one type of effective stimulus only has been presented. In the present case, however, as outlined, many types of stimuli were effective for the production of convulsive responses. Wilson [20] studied a similar case, but to my knowledge no case has been reported in which attacks could be produced simply by movement. Thus, the relation of movement to the production of a convulsive seizure should be discussed. In my case only the movements of the right side, and only those of a special type, were effective in the production of convulsive symptoms. The effective movements were those which had to be performed with special attention of the patient directed toward the performance. Attention in itself as the effective stimulus was ruled out, however, because the performance of the same movements on the left side or the prolonged fixation of attention by tasks requiring no motor reaction was not effective for the provocation of an attack. It is interesting to note the difference in the effect of isolated movements and that of the same movements as part of a daily life activity in the production of an attack. This difference indicates a marked dissimilarity in the central

17. Metzger, E.: Experimentelle Untersuchungen über den Lichttonus des Menschen und des Kaninchens, Arch. f. Ophth. **127**:296, 1931.

18. Schaffer, K.: Suggestion und Reflex: Eine kritische experimentelle Studie über die Reflexphaenomene des Hypnotismus, Jena, Gustav Fischer, 1895.

19. Fulchignoni, E.: Contributo alla conoscenza dell epilessia sperimentale riflessa per stimoli luminosi, Riv. di pat. nerv. **51**:1, 1938.

20. Wilson, S. A. K.: Morison Lectures on Nervous Semeiology with Special References to Epilepsy, Brit. M. J. **2**:1, 50 and 90, 1930.

mechanisms underlying these two types of performance. Such differences are known also from the studies on apraxia, and they again confirm Goldstein's [21] opinion concerning the significance of the "total situation." The difference in the effect of unaccustomed movements and that of movements which were learned also indicates that there must be dissimilar central mechanisms underlying these two responses. Differentiation of constructive and idiokinetic apraxia, first made by Kleist [22] and me,[23] also shows that fundamental differences exist between the central mechanism for learned movements and that for movements to be performed for the first time. Either of these two types of movement can be affected alone by lesions in distinct locations of the brain. Thus, the result of this study confirms the opinion as to the physiologic differences between these two types of movement. The differences are sufficient to produce even unlike convulsant effects from the two types of movement.

Confirmation of some of the findings in the present case come from many experiments, including those of Amantea,[24] Baglioni,[25] Buscaino,[26] Clementi,[27] Fulchignoni,[19] Gozzano [28] and Spiegel.[29] By the local application of strychnine to the cortex, increased excitability of certain parts was produced. Subsequent stimulation of the peripheral end organs corresponding to these cortical lesions induced convulsive seizures.

The effect of cocaine in the present case is exceedingly interesting. It was originally administered to eliminate any possible stimulation of conjunctiva and cornea when the effectiveness of light stimulation was tested. Elimination of these stimuli by cocaine produced a change in the effectiveness of all the other convulsion-producing stimuli. This fact would suggest that in illness elimination of focal stimuli may have a far reaching effect and that from the theoretic and practical therapeutic points of view, one should be constantly aware of such possibilities.

Fulchignoni [19] recently reported on the following experiment on a dog: After strychninization of the occipital cortex convulsive seizures

21. Goldstein, K.: Der Aufbau des Organismus, The Hague, Martinus Nijhoff, 1934.

22. Kleist, K.: Gehirn-Pathologie vornehmlich auf Grund der Kriegserfahrungen, in Handbuch der ärztlichen Erfahrungen im Weltkriege, Leipzig, Johann Ambrosius Barth, 1934, vol. 4, pt. 2.

23. Strauss, H.: Ueber konstruktive Apraxie, Monatschr. f. Psychiat. **56**:65, 1924.

24. Amantea, G.: Sur les rapports entre les centres corticaux de la circonvolution sigmoïde et la sensibilité cutanée chez le chien, Arch. ital. di biol. **63**:143, 1915.

25. Baglioni, S.: Il metodo della locale stimolazione chimica nello studio dei centri corticali, Arch. di farmacol. sper. **17**:302, 1914.

26. Buscaino, V. M.: Die experimentelle Epilepsie aus afferenten Reizen, Folia neuropath. estoniana **15**:126, 1936.

27. Clementi, A.: Sfera gustativa della corteccia cerebrale del cane ed epilessia sperimentale riflessa a tipo sensoriale gustativo, Boll. d. Soc. ital. di biol. sper. **10**:902, 1935.

28. Gozzano, M.: Bioelektrische Erscheinungen bei Reflexepilepsie, J. f. Psychol. u. Neurol. **47**:24, 1936.

29. Spiegel, E. A.: Rindenerregung durch Labyrinthreizung, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:178, 1932.

were provoked by light. When a preparation of cocaine was instilled into the conjunctival sac of the eye on the side opposite the strychninized hemisphere, light no longer provoked a seizure. Here, again, the elimination of stimuli from one set of receptors influenced the convulsant effect of stimuli from a second set of receptors.

After repeated experiments with cocaine, distributed over four months, the possibility of inducing reflex seizures disappeared completely. Even several months after the last application of cocaine no reflex seizures could be obtained. This prolonged effect indicates that a therapeutic procedure directed along the line of temporary elimination of stimuli may produce prolonged readjustment of the central nervous mechanism, even in organic disturbances. As already noted, not only were the experimentally produced seizures eliminated by cocaine but there was also a favorable influence on the apparently spontaneous attacks and those produced by hyperventilation.

The exact action of the cocaine is not clear, but the following theoretic explanations may be given: The cortical center of conjunctival and corneal sensibility is the primary focus of the convulsive phenomena. From this focus the wave of pathologic excitation spreads to other portions of the brain, especially the motor cortex of the left hemisphere. The pathologic state of excitation of the primary focus is maintained by the constant flow of peripheral stimuli to this center. Elimination of these stimuli, therefore, reduces the excitation of this center to a degree below that sufficient for the production of convulsive phenomena. In addition, temporary interruption of the flow of stimuli to this primary center induces a period of rest after many years of daily pathologic stimulation, thus allowing a decrease of excitability of long duration. This would be in opposition to the observations originally made by Gowers,[30] and later by Foerster,[31] that one epileptic attack creates the condition for the next.

The case under discussion is not common. No exactly similar case to my knowledge has been reported, and generalization from one case cannot be made. However, every abnormal observation reveals mechanisms which have been brought into special evidence by the pathologic process in the particular case. Thus, it would seem to be important that more attention than is usually given should be paid to the role of peripheral stimuli in the provocation of attacks in epileptic patients. The effects of these stimuli should be noted not only by purely clinical observation but also, if possible, by electroencephalographic studies on the patient, with the purpose of determining whether the same peripheral stimulus exerts an influence on the electroencephalogram of the normal person differing from its effect on that of the epileptic patient. It is also advisable to attempt in any case to improve the condition of the patient by elimination of certain peripheral stimuli. The problem arises as to the point of the body at which this should be done. The region in which a favorable effect might most probably be expected would be the region where the first twitching or the first symptoms of the aura appear.

30. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Disorders, London, J. & A. Churchill, 1901.

31. Foerster, O.: The Cerebral Cortex in Man, Lancet **2**:309, 1930.

Mondio [32] has reported some success in this direction. It is not necessary, however, that the point at which the first overt symptoms begin should correspond with that at which elimination of stimulation can be performed with the greatest chance of success. Electroencephalograms may well help one to discover from which point of the brain the pathologic excitation originates and, in turn, to trace the corresponding peripheral locus where therapeutic transference might be performed most successfully.

SUMMARY

1. A case is described in which jacksonian seizures could be induced on the right side by various stimuli and movements on the same side.

2. A study has been made of the characteristics of the effective stimuli and movements.

3. Application of cocaine to the conjunctival sac of the right eye diminished the number and intensity of the reflex convulsions. The effect was both immediate and permanent. The spontaneous seizures of the patient were also favorably influenced by this procedure.

4. Conclusions are drawn as to the differences and relations between certain types of "voluntary" movements.

5. The importance of this observation for the theory and treatment of epilepsy in general is discussed.

6. Electroencephalographic studies of the patient are described.

32. Mondio, E.: Epilessia da iperpnea ed epilessia riflessa nell'uomo, Riv. di pat. nerv. **39**:156, 1932.

TERATOMA OF THE PINEAL BODY

A Clinicopathologic Report*

BEN W. LICHTENSTEIN, M.D., CHICAGO

The occurrence of a teratomatous tumor in the pineal body of a female is very rare, only 1 instance being recorded in the literature (Luce [1]). The case to be reported is unusual both because of the large size of the tumor and because of its occurrence in a girl aged 6 months, who clinically presented the picture of slowly, progressively developing internal hydrocephalus.

REPORT OF A CASE

History.—A white girl was admitted to the pediatric division of the Cook County Hospital on Jan. 26, 1937. She was born on Aug. 25, 1936, after a labor that lasted ten hours and was uneventful. Soon afterward, the child began to vomit after feeding, and she was taken to a nearby hospital, where bilateral ventricular puncture and lumbar puncture were done, with insertion of dye into one of the lateral ventricles. This showed free communication between the lateral ventricles but none with the spinal subarachnoid sac. When iodized poppyseed oil was instilled into one lateral ventricle, roentgenograms revealed a complete block between the third ventricle and the aqueduct of Sylvius. The child was discharged with a clinical diagnosis of congenital atresia of the aqueduct of Sylvius. At home, enlargement of the head and vomiting continued, and despite ventricular tappings the child did poorly and died.

Necropsy.—The anatomic diagnoses were teratoma of the pineal body, with compression of the aqueduct of Sylvius and marked internal hydrocephalus; focal bronchopneumonia in the right lower pulmonary lobe; empyema of the right pleural cavity; parenchymatous degeneration of the myocardium, the liver and the kidneys, and marasmus.

Macroscopic Observations.—The essential pathologic condition was in the cranium. The brain was greatly enlarged; its convolutions were widened and flattened, and the sulci in many places were obliterated. The cerebellum and the brain stem were grossly normal, but the cerebral cortex was very thin. After fixation in solution of formaldehyde the brain was cut into coronal sections. Arising from the region above the quadrigeminal plate and extending anteriorly to the rostral portion of the septum pellucidum was an irregular, firm multicystic mass composed of two lobes (fig. 1). This mass completely filled the third ventricle and bulged into both lateral ventricles, especially the right. The larger of the lobes was on the right side and measured 7 cm. in its greatest vertical

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* The case reported has been described as case 92 by Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

1. Luce, H.: Zur Diagnostik der Zirbelgeschwülste und zur Kritik der cerebralen Adipositas, Deutsche Ztschr. f. Nervenh. **68**:187, 1921.

and 6 cm. in its greatest transverse diameter. The ependymal lining covering the mass was thin, smooth and only loosely attached to it. The smaller lobe measured 5 cm. in its greatest vertical and 4.5 cm. in its greatest transverse diameter. It completely filled the third ventricle and bulged through the greatly dilated foramen of Monro into the left lateral ventricle. The two lobes were connected by a bridge of tissue which measured up to 10 mm. in thickness. The tumor was composed of firm tissue which varied from pinkish gray to grayish brown. The left lobe was chiefly solid and homogeneous, while in the right lobe there were numerous cysts ranging from the size of a pinpoint to 2.5 by 1.2 cm. The

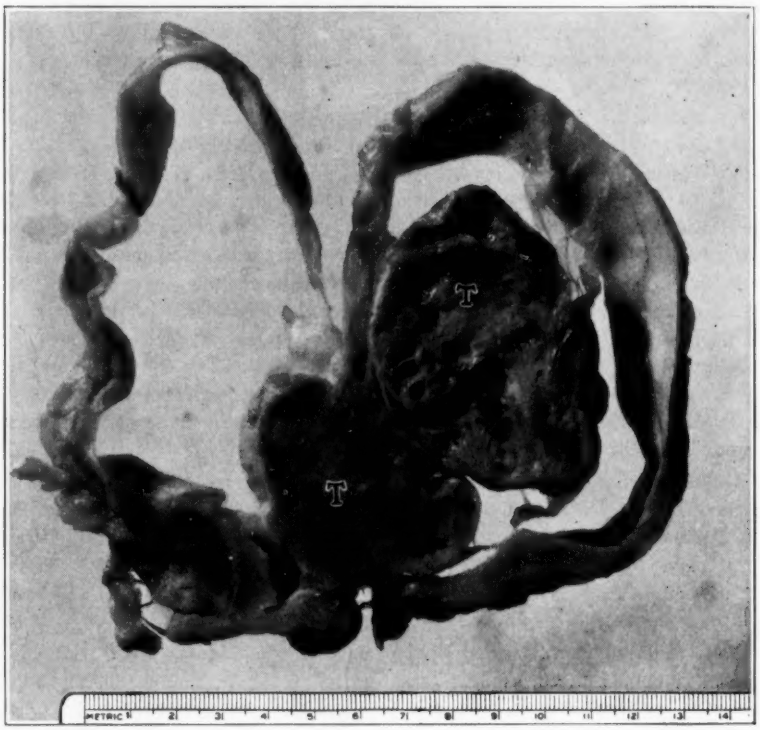

Fig. 1.—Photograph of a coronal section of the brain fixed in solution of formaldehyde. *T*, pineal tumor.

cysts were filled with clear, colorless fluid. The columnae fornicis and the corpus callosum were much flattened and were adherent to the tumor. The lateral ventricles were tremendously dilated; the cerebral cortex on the left side varied from 1 to 4 mm. in thickness and on the right side from 2 to 5 mm. The basal ganglia and the internal capsule on both sides were much flattened. The rostral end of the aqueduct of Sylvius was narrowed and flattened; its lumen was patent throughout. The fourth ventricle was not dilated, and the pineal body was not found.

Microscopic Observations.—The larger node contained a variety of histoid structures (fig. 2), among which epithelial elements predominated. There were

islands of stratified squamous epithelium (epidermoid), with a moderate degree of keratosis. In focal areas hair follicles were observed. Epidermoid cysts, which varied considerably in size, were common. In many places the epithelium lining these cysts was piled up several cell layers in thickness, and the content was composed of desquamated epithelial cells. Other cysts were lined by granular

Fig. 2.—Low power photomicrograph of the tumor containing a variety of histoid structures. *B,* bone; *C,* cartilage; *C.T.,* connective tissue; *Cy.,* cysts; *Sq.E.,* squamous epithelium. Van Gieson's stain.

epithelium, its cells being high columnar and mucus producing. Here and there the epithelium was papillary and several cell layers in thickness, and the subepihtelial tissue was composed of very cellular embryonal mesenchymal tissue. The content of the cysts was amorphous material containing single polymorphonuclear leukocytes and chromatin debris. Other cysts were filled with homogeneous colloid-like material which stained deep orange by Van Gieson's method. In some

places organoid structures resembling intestine were seen. These consisted of many mucus-producing glands overlying a densely cellular mesenchymatous stroma, which in turn lay on a stroma which was loose and fibrillar. This mucosa and submucosa was enveloped by two distinct layers of smooth muscle, an inner layer of circular fibers and an outer layer of longitudinal fibers. In other places the epithelium closely resembled that of the upper respiratory passages, and islands of

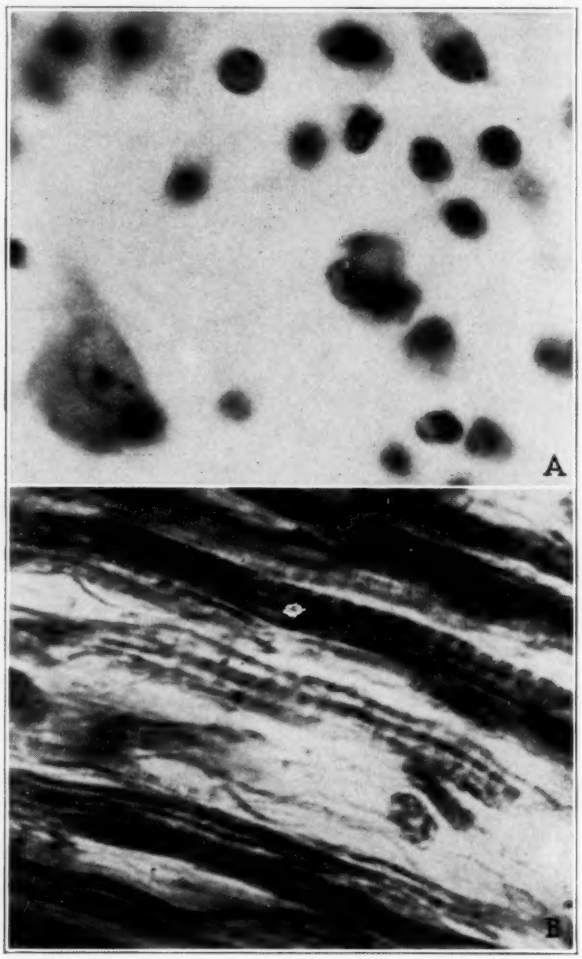

Fig. 3.—*A*, high power photomicrograph showing a neural portion of the tumor containing ganglion and glia cells. Toluidine blue stain. *B*, high power photomicrograph showing bundles of striated muscles. Mallory's phosphotungstic acid—hematoxylin stain.

cartilage and bundles of smooth muscle fibers gave the structures a bronchus-like appearance.

Mesodermal derivatives were plentiful, in the form of islands of cartilage, fat tissue and striated muscle (fig. 3 *B*). There were islands of both cartilaginous

and membranous bone formation (fig. 2), and between the bony trabeculae were thin-walled blood vessels and islands of active bone marrow.

Neurogenic elements were present in a variety of histoid forms, the most prominent being neuroepithelial tubules (fig. 4) composed of large cells with an ample amount of cytoplasm and large oval vesicular nuclei. The inner border of the cells was the site of a distinct cuticular membrane, and there were granules of blepharoplasts just beneath it. In other places there were structures resembling

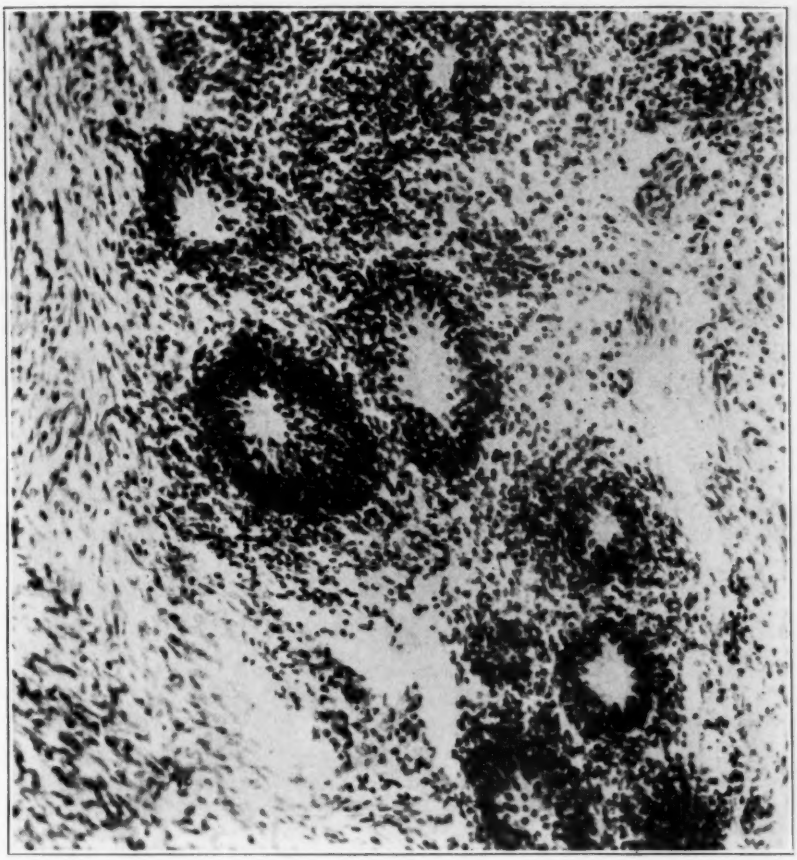

Fig. 4.—High power photomicrograph showing neuroepithelial structures. Toluidine blue stain.

medullary epithelium. Much of this was arranged in the form of tubules, the cells being columnar and hyperchromatic. Innumerable cilia protruded into the lumen from the lining cells. The cells subjacent to the lining layer were hyperchromatic and closely packed. This embryonal neural tissue was in many places fairly well separated from the subjacent tissues by accumulations of elongated spindle-shaped fibrocytes, which gave this covering the appearance of a rudimentary leptomeninx. In addition to the embryonal nerve tissue there were focal accumulations of large, fully developed ganglion cells, each of which was enveloped by a zone of capsule cells simliar to that seen in the spinal ganglia.

The smaller node was composed almost exclusively of brain tissue. It consisted of a mosaic of cell groups which varied considerably in size. The majority of the cells in these cellular accumulations were large, with vesicular nuclei rich in chromatin material and with an ample amount of pale-staining cytoplasm. Scattered among these larger cells were smaller ones with round, pyknotic and densely hyperchromatic nuclei. These cell groups were enveloped by loosely scattered gliocytes, among which were occasional ganglion cells (fig. 3 *A*) and irregular calcareous concentrations. This node contained capillaries and larger blood vessels, some of which showed subendothelial calcification.

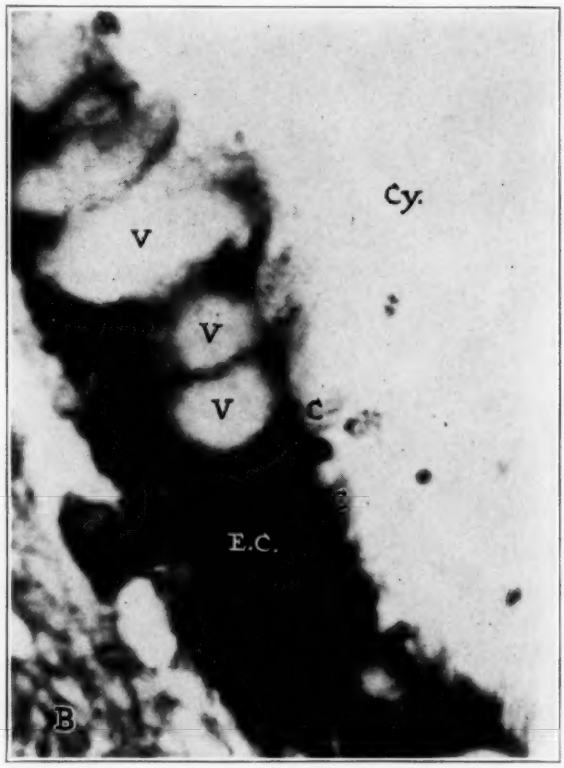

Fig. 5.—High power photomicrograph of the lining of an ependymal cyst. *B*, brain; *E.C.*, ependymal cells; *C.*, cilia; *Cy.*, cyst; *V*, vacuoles. Heidenhain's iron hematoxylin stain.

In close relation to the brain tissue were many cysts lined by a single layer of ciliated high columnar epithelium (fig. 5). Many of the cells contained large clear vacuoles; in places these vacuoles were ruptured, and their contents were discharged into the cyst cavity.

COMMENT

Pathologic Considerations.—From the histologic description it is evident that the tumor in this case consisted of tissues derived from the three primitive germ layers and that it may be termed, therefore,

a teratoma. Whereas many of the structures, such as the bone, cartilage and muscle, were adult, some of the neurogenic elements were definitely embryonic. It is well known that the midline of the developing embryo has great potentialities for misplacement and subsequent maldevelopment of cells and that the character of the resultant new growths necessarily depends on the potentialities of these cellular inclusions. In addition to the pineal body, teratomas have been found in other midline structures of the brain, such as the third ventricle (Saxer [2]), the pituitary gland (Kon [3]), the tuber cinereum (Bosco [4]) and the parapineal region (McLean [5]), as well as the cerebellum (Hosoi [6]). In a review of 41 cerebral teratomas and teratoid tumors by Hosoi,[6] 18 were found to occur in the pineal body alone. Krabbe [7] was of the opinion that the pineal body is a frequent site of teratoma because during intrauterine life the germ of the gland comes very near the surface, facilitating the penetration of foreign tissue elements. In sharp contrast to teratoma in the brain, all of the comparable new growths in the spinal cord have been teratoid or bigerminal, with an absence of entodermal derivatives (Hosoi,[8] Bucy and Buchanan [9]).

As in most embryonal tumors, hornifying squamous epithelium was abundantly present—anlages of the central nervous system, in the form of medullary epithelium similar to that reported by Klapproth [10] as occurring in a teratoma of the pineal body, were present, as well as well formed brain tissue of an adult type and peripheral ganglion cells enveloped by capsule cells. Bundles of striated muscles were found, as in the cases of Neumann [11] and Frank,[12] and smooth muscle was present as a component part of the intestinal and respiratory system

2. Saxer, F.: Ein zum grössten Theil aus Derivaten der Medullarplatte bestehendes grosses Teratom in III. Ventrikel eines 7 wöchentlichen Kindes, Beitr. z. path. Anat. u. z. allg. Path. **20**:399, 1896.

3. Kon, J.: Hypophysenstudien: I. Seltene Tumoren der Hypophysengegend (Teratom, Peritheliom, telangiektatisches Sarcom), Beitr. z. path. Anat. u. z. allg. Path. **44**:233, 1908.

4. Bosco, G. A.: Teratoma del región del tuber cinereum, Proc. Pan-Am. Scient. Cong. **10**:522, 1917; cited by Hosoi.[6]

5. McLean, A. J.: Pineal Teratomas with Report of a Case of Operative Removal, Surg., Gynec. & Obst. **61**:523, 1935.

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complexes. That this teratoma was a tumor of the pineal body is evidenced by localization of the growth just above the quadrigeminal plate. It is well known that a large tumor of such a small organ as the pineal body may in its evolution completely destroy the primordial pineal tissue or may include it within its structures. Whereas the larger of the two nodes was composed almost exclusively of teratomatous tissue, the small one had a mosaic structure the cells of which in places bore a resemblance to those of the pineal body. The amount of such tissue present was much more than in the normal epiphysis, and in this respect the tumor resembled that in the case reported by Klapproth,[10] in which a teratoma of the pineal body was present, combined with an adenoma of that organ.

Of unusual interest were the cysts lined by high columnar ciliated epithelium. In teratomatous tumors it is almost impossible to tell of which tissues in the adult organism these cysts may be a part. The close relation of these cysts to brain tissue and their microscopic appearance led me to believe that their lining cell represented ciliated fetal ependyma. Rosenthal [13] described an intramedullary tumor of the spinal cord, which he called a neuroepithelioma gliomatosum microcysticum. It contained multiple cysts and canals which were lined by cylindric epithelium, on the free border of which occasional cilia were seen. Kubie and Fulton,[14] in a study of similar teratomatous cysts of the spinal cord, came to the conclusion that they represented ciliated fetal ependyma and that they might have arisen by extramedullary outpocketing of the central canal. The occurrence of cilia in the lining epithelium of ependymal cysts has been described by Byrom and Russell [15] and others. The presence of secretory globules in the lining cells and the rupture of some of these into the cyst cavity bore a striking resemblance to the development of ependymal cysts.

Clinical Considerations.—From the first report of a teratoma of the pineal body by Weigert [16] (1875) to publication of the present case, such a tumor has occurred in a female in only 1 instance. The relative immunity of the pineal body of the female to tumors in general and to teratomas in particular has had no satisfactory explanation. Because of the enormous size of the tumor at necropsy and the onset of obstructive hydrocephalus immediately after birth, it may be safe to presume that the tumor had already been present in utero. In this respect the case is similar to those reported by Schuster [17] and Hulst,[18] in which

13. Rosenthal, W.: Ueber eine eigenthümliche, mit Syringomyelie complizierte Geschwulst des Rückenmarks, Beitr. z. path. Anat. u. z. allg. Path. **23**:111, 1898.

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the hydrocephalus already present in utero produced dystocia. In Schuster's case the enlarged head burst during delivery, and in the escaping cerebrospinal fluid a teratoma enveloped by a thin layer of brain tissue was found. In Hulst's case a similar teratoma was delivered when the head burst during traction. The exact site of origin of the teratoma in these 2 cases could not be determined because of the extreme disorganization of the brain substance. It is interesting to note that the block between the third ventricle and the aqueduct of Sylvius, as demonstrated by intraventricular instillation of iodized poppyseed oil, was interpreted as due to congenital atresia of the aqueduct. Pneumoencephalographic examination was not attempted; this is unfortunate, for it might have outlined the tumor mass in addition to demonstrating the aqueductal block. The frequent occurrence of pubertas praecox in cases of tumor of the pineal body is well known. Askanazy [19] expressed the opinion that only teratomas of the pineal gland are associated with somatic or sexual precocity. Neither external nor internal evidences of precocious sexual development were present in this case, but the extreme youth of the infant precluded any far-reaching generalizations concerning this important matter. The literature on teratomas of the pineal body has recently been reviewed by Bochner and Scarff.[20]

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DERMOID TUMOR IN THE FORAMEN MAGNUM, WITH ASTEREOGNOSIS AND DISSOCIATED SENSORY LOSS

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Tumeurs perlées, as described by Cruveilhier [1] in 1829, are among the more rare intracranial neoplasms, comprising less than 1 per cent of the total number of the latter. The use of the term dermoid or epidermoid [2] is preferable to that of cholesteatoma, as it indicates the epithelial nature of the tumors and distinguishes them from the "cholesteatomas" of middle ear origin. Their lustrous "mother-of-pearl" appearance makes them easy to recognize. Not infrequently they are cystic. Epidermoids differ from dermoids in that they contain only squamous or basal epithelium, while dermoids also have epithelial appendages, such as hair and sebaceous glands. Approximately 150 cases of pearly tumors have been reported in the literature; the location was chiefly in the pia mater at the base of the brain. Chiasmal syndromes occur; the tumor may extend into the cerebellopontile angle, or, as in 2 of Cushing's cases reported by Bailey,[3] it may lie in the foramen magnum.

Extramedullary tumor in the foramen magnum may produce dissociated sensory loss. Cushing,[4] Roussy and Lévy [5] and Rubinstein [6] noted loss of position sense and two point discrimination with astereognosis in the affected hand, with sparing of superficial sensation for pain, touch and temperature. Adson, Kernohan and Woltman [7] found a similar type of dissociation in a patient with a chordoma arising from the nasopharynx, in the region of the second cervical vertebra. Our patient showed loss of position sense in the affected limbs, astereognosis and faulty two point discrimination. Superficial sensation for touch, pain and temperature together with vibratory sense, was unaffected.

From the Neurological Service of the Mount Sinai Hospital.

Read before the New York Neurological Society, Dec. 5, 1939.

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5. Roussy, G., and Lévy, G.: Existence d'une dissociation dite corticale des troubles de la sensibilitié, Rev. neurol. **1**:145, 1930.

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REPORT OF A CASE

Stiffness of the neck, vomiting, ataxia, diplopia, blurring of vision, vertigo and clumsiness of the right hand for fourteen months. Absence of position sense in the fingers and toes on the right side. Astereognosis and loss of two point discrimination in the right hand. Preservation of pain, touch, temperature, and vibratory sensation. Suboccipital craniotomy with partial removal of a tumor compressing the medulla. Bronchopneumonia; death; necropsy.

History.—B. L., an unmarried white woman aged 40, a librarian, was admitted to the Mount Sinai Hospital on Oct. 6, 1938. Fourteen months previously she had begun to notice progressive stiffness of the neck and shoulders, accompanied by episodes of vomiting. For twelve months she had walked with a "drunken" gait, veering to the right. There was increasing clumsiness in the use of the right hand, with difficulty in grasping and manipulating objects. She also complained of occasional blurring of vision, diplopia and spells of vertigo. She had lost 14 pounds (6.4 Kg.) in weight.

Examination.—On admission the patient was thin and appeared chronically ill. General physical examination showed slight enlargement of the thyroid, but no evidence of exophthalmic goiter. A soft systolic apical murmur was heard. The blood pressure was 134 systolic and 74 diastolic. The patient was alert, and the mentality was well preserved.

Neurologic examination revealed that the patient held her head stiffly and inclined to the right. She veered to the right in walking and slapped her right foot down in an awkward fashion. There was slight tenderness to pressure over the second cervical spine. Motor power was good, there being only slight weakness of the right upper extremity. Deep hyperreflexia was present bilaterally, being greater on the right than on the left. There were no spasticity and no pathologic reflexes. The abdominal reflexes were absent. The right extremities were severely ataxic, with a slight rebound phenomenon in the right arm. The ataxia appeared to be chiefly of the sensory type. Sensory examination showed that superficial pain, touch and temperature sensibility were intact, except for questionable hypesthesia over the palm of the right hand. Position sense was lost in the fingers and toes on the right side, and was occasionally defective in the digits of the left extremities. Vibration sense was not disturbed. There was astereognosis in the right hand, with loss of two point discrimination. In addition to inability to recognize objects, the patient was unable to distinguish rough objects from smooth. Weights were poorly calculated with the right hand. Examination of the cranial nerves showed normal fundi, moderate dilation and equality of the pupils, coarse rotary nystagmus on lateral gaze, slight weakness of the right external rectus muscle and marked diminution of the right corneal reflex.

Laboratory Data.—Examination of the blood showed a hemoglobin content of 73 per cent, 4,500,000 red cells and 11,200 white cells. Lumbar puncture yielded clear fluid, with a normal protein content and no cells. The initial manometric pressure was 150 mm. of water, with no evidence of block. A roentgenogram of the cervical portion of the spine showed slight osteoarthritis. Ventriculographic studies showed dilatation of the ventricular system, ending abruptly at the iter.

Operation.—Suboccipital craniotomy was performed on October 17 by Dr. Ira Cohen, and a cystic neoplasm was partially removed. The tumor compressed and surrounded the right half of the medulla, extending from the second cervical

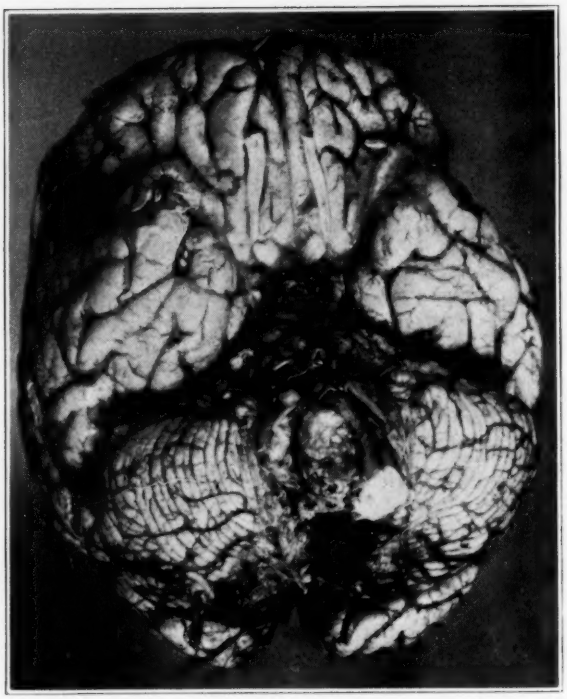

Fig. 1.—Gross appearance of the brain at necropsy.

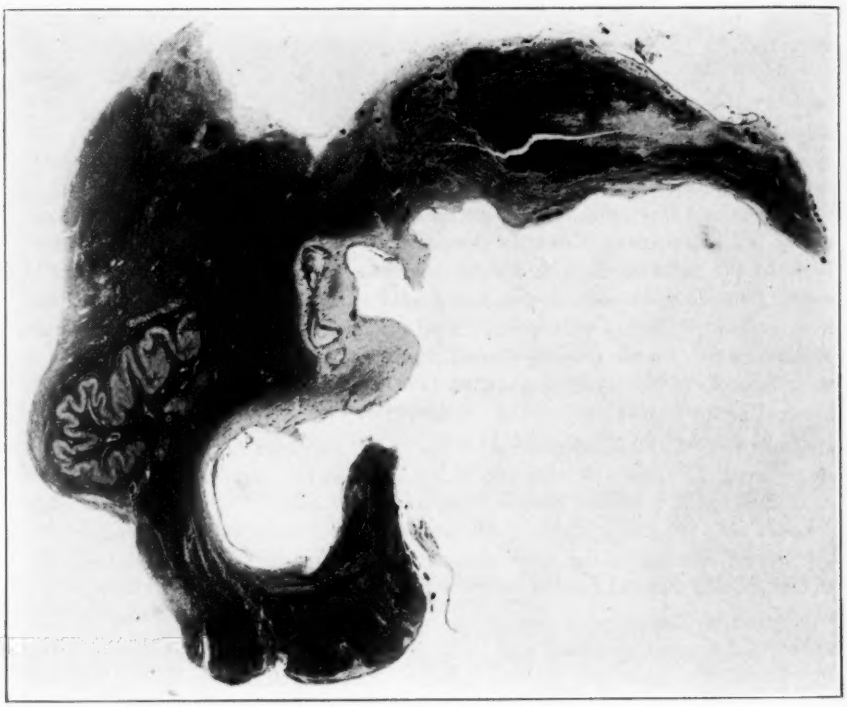

Fig. 2.—Section through the middle of the olive, showing demyelination of the inferior cerebellar peduncle. Weil stain.

spine up through the foramen magnum into the fourth ventricle, where it was adherent to the floor. The vermis and cerebellar hemispheres were displaced upward.

Course.—The immediate postoperative course was favorable, but bronchopneumonia developed and the patient died eight days after operation.

Gross Anatomic Observations.—Internal hydrocephalus was present above the middle of the aqueduct. A large cystic neoplastic mass, 4.5 by 2.5 cm., was

Fig. 3.—Section through the lower portion of the olive, showing compression of the medial lemnisci and destruction of the right inferior olive and the descending tract of the fifth nerve. Weil stain.

situated on the right side and compressed and displaced the medulla (fig. 1). The tumor was firm and pearly white and was covered with excrescences. It was easily enucleated from its bed. The right vertebral artery was stretched over its ventral surface. At the level of the lower third of the olive, the brain stem appeared as a narrow crescentric rim of tissue surrounding the tumor. The fourth ventricle was dilated. The vermis was softened and hemorrhagic.

Microscopic Anatomic Observations.—Section of the cyst wall showed a layer of connective tissue underlying its free surface, with an inner epithelial lining. The epithelial cells were of the squamous and cuboid type, with hornification. The connective tissue layer contained a variety of tissues, including bone, cartilage and structures having the characteristics of hair follicles and sebaceous glands.

Serial sections through the brain stem were prepared by the Weil and Nissl methods. The most severe damage was sustained at the level of the middle of the olive (fig. 2), where the bulb was reduced to a thin shell about the tumor. The

Fig. 4.—Section at the level of the pyramidal decussation showing marked compression of the dorsal columns. Weil stain.

structures of the right side of the medulla were not distinguishable, except for the flattened remnants of the medial lemniscus and the pyramid. In sections through the lower end of the olive (fig. 3), the pyramids were displaced and showed demyelination. The medial lemnisci were also severely compressed. Only a fragment of the right inferior olive could be seen. At the caudal end of the medulla (fig. 4) the dorsal columns were compressed, but did not show demyelination. The spinal tract and nucleus of the fifth nerve appeared to be damaged. Just lateral and dorsal to the right pyramid were intact fiber bundles, probably containing the lateral spinothalamic and ventral spinocerebellar tracts.

At the rostral end of the medulla (fig. 5) there had been less compression. The cavity of the tumor was seen just ventrolateral to the right inferior cerebellar peduncle, which was flattened and showed demyelination, with hemorrhages and round cell infiltration. The cells of the right spinal and medial vestibular nuclei displayed degenerative changes. In contrast to other structures in the right inferior cerebellar peduncle the entering right olivocerebellar tract was intact. The left olivocerebellar fibers were few, as might be expected from the involvement of the right olive. The medial lemnisci in the upper portion of the medulla and pons did not show ascending degeneration. Sections of the region of transition between the cervical portion of the cord and the medulla indicated slight descending degeneration of the pyramids.

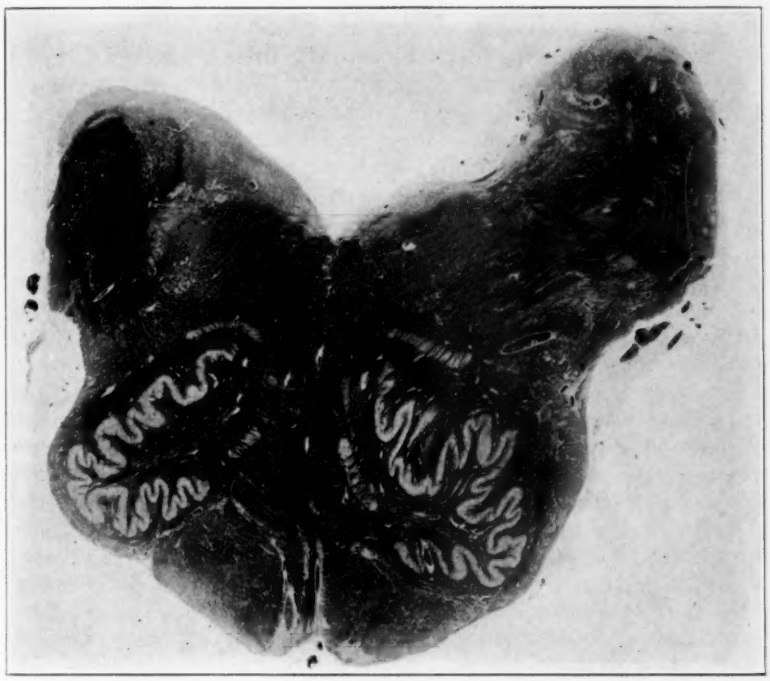

Fig. 5.—Section through the rostral end of the medulla. Weil stain.

COMMENT

Anatomically, the pathways of the right half of the medulla were so severely compressed that all conduction must apparently be interrupted. However, the preservation of the medial lemnisci at higher levels indicated the maintenance of function. Likewise, the pyramids showed only slight descending degeneration. Apparently, these structures had accommodated themselves to the effects of long-standing pressure and crowding by the tumor. More damage was sustained by the right olive, the right descending tract of the fifth nerve and the tracts entering the cerebellum. Except for the right olivocerebellar tract, the structures in the right inferior cerebellar peduncle showed extensive

demyelination. The number of olivocerebellar fibers entering the left restiform body was reduced, indicating the lesion at their source in the right olive.

The vertigo and nystagmus appeared as manifestations of the damage to the vestibulocerebellar system. The marked diminution of the right corneal reflex is attributable to involvement of the descending tract of the trigeminal nerve. Superficial touch and vibratory sensations were not clinically involved, despite compression of the dorsal columns and the medial lemnisci. Pain and temperature sensations were preserved in the intact lateral spinothalamic tract, just dorsolateral to the pyramid. Worthy of note was the absence of Horner's syndrome.

Astereognosis, loss of position sense and two point discrimination and difficulty in estimating weights are generally attributed, and correctly so, to lesions of the parietal lobe, since these qualities are regarded as being of the discriminative cortical type.[8] The astereognosis reported by Cushing and others in cases of tumor of the posterior fossa was, like that observed with cortical lesions, invariably accompanied by disturbances in position sense and two point discrimination. It is these modalities that are concerned with appreciation of the spatial relationships of the limbs and with the discrimination of weights, and that have the most important representation in the cerebral cortex. It would appear that the fine proprioceptive adjustment and motor integration inherent in the application of these qualities require a cerebellar component. The exact role of the cerebellum in that adjustment is not clear, however. Holmes[9] did not find any actual loss of position sensation in cases of purely cerebellar lesions. He noted some defect, however, in the estimation of weights, the patient usually perceiving the object as being heavier than it actually was. This may be related to barognosis, which is regarded as a cortical modality. Thus, it seems that there is a cerebellar factor in what are considered cortical functions.

Anatomically, there is evidence to substantiate the assumption that stereognostic, barognostic and proprioceptive impulses to the thalamus and cortex have a cerebellar component, in addition to that conveyed by the posterior columns and medial lemnisci. From the gracile and cuneate funiculi, especially the latter, a fiber bundle travels to the vermis of the cerebellum via the external cuneate nucleus and the inferior cerebellar peduncle (von Monakow,[10] Mussen[11] and Ferraro and Barrera[12]). From the dentate nucleus the superior cerebellar peduncle carries fibers to the lateroventral nucleus of the thalamus, which sends

8. Holmes, G.: Disorders of Sensation Produced by Cortical Lesions, Brain **50**:413, 1927.

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12. Ferraro, A., and Barrera, S. E.: Posterior Column Fibers in Monkeys, J. Comp. Neurol. **62**:507, 1935.

projections to cortical areas 4 and 6 of Brodmann (Clark and Boggon,[13] Clark[14] and Walker[15]). Poliak[16] expressed the belief that the agranular portion of the precentral cortex is a somatosensory region, probably associated with proprioceptive function. Bard[17] demonstrated that preservation of area 4 is necessary for maintenance of the proprioceptive placing and hopping reactions in the monkey.

In the case under discussion, while the posterior columns and medial lemnisci were compressed, their function was not completely interrupted, as evidenced clinically by the preservation of vibratory sensation. The additional damage to the cerebellar connections was apparently necessary to produce the defect in kinesthetic and stereognostic sensation. The loss of position sense with preservation of vibratory sensibility is of interest in view of the fact that these modalities seemingly are carried in the same tracts. Dissociated disturbance of kinesthesia and pallesthesia, however, has been noted. It is well known that with cortical lesions position sensation may be markedly affected while vibration is little, if at all, involved (Head and Holmes,[18] Marie and Bouttier[19] and Wechsler[20]). In the 2 cases of tumor of the foramen magnum with astereognosis reported by Rubinstein,[6] there was greater involvement of position than of vibratory sense in the affected extremities.

Although the sensations of vibration and position often are grouped together as related aspects of deep sensibility, their functions are quite different. Vibratory sense hardly enters into the appreciation of spatial relationships and probably has little proprioceptive connection with the cerebellum. The suggestion is therefore made that loss of position sense with preservation of vibratory sensation occurs when lesions of the posterior columns affect predominantly their cerebellar projections.

SUMMARY

1. A case of dermoid tumor in the foramen magnum, with partial operative removal and necropsy, is reported.

2. Clinically, there were ipsilateral astereognosis, loss of the sense of position and two point discrimination and preservation of superficial pain, touch and temperature sensibility. Vibratory sensation was intact.

13. Clark, W. E. L., and Boggon, R. H.: The Thalamic Connections of the Parietal and Frontal Lobes of the Brain in the Monkey, Phil. Tr. Roy. Soc., London, s.B **224**:313, 1935.

14. Clark, W. E. L.: The Connections of the Arcuate Nucleus of the Thalamus, Proc. Roy. Soc., London, s.B **123**:166, 1937.

15. Walker, A. E.: An Experimental Study of the Thalamo-Cortical Projections of the Macaque Monkey, J. Comp. Neurol. **64**:1, 1936.

16. Poliak, S.: The Main Afferent Fiber Systems of the Cerebral Cortex in Primates, Berkeley, Calif., University of California Press, 1932.

17. Bard, P.: Studies on the Cortical Representation of Somatic Sensibility, in Harvey Lectures, 1937-1938, Baltimore, Williams & Wilkins Company, 1938, vol. 33, p. 143.

18. Head, H., and Holmes, G.: Sensory Disturbances from Cerebral Lesions, Brain **34**:102, 1911.

19. Marie, P., and Bouttier, H.: Études cliniques sur les modalitiés des dissociations de la sensibilitié dans les lesions encephaliques, Rev. neurol. **38**:1, 1922.

20. Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 3, Philadelphia, W. B. Saunders Company, 1935.

3. Anatomically, the tumor caused marked distortion of the medulla, with marked flattening of the posterior columns and nuclei, but without demonstrable ascending degeneration of the medial lemnisci. There was demyelination of the right inferior cerebellar peduncle. The right olive and the descending tract and nucleus of the fifth nerve were also affected. The pyramidal tracts were compressed and showed slight descending degeneration.

DISCUSSION

DR. H. A. RILEY, New York: I have battled so frequently, and apparently so unsuccessfully, for what seems to me the proper interpretation and use of the term astereognosis that I am somewhat discouraged with the prospect of ever recurring engagements. Nevertheless, I feel impelled to take up again the question which has been posed by the presentation this evening. I must confess, however, that the suggestion made by Dr. Weinstein and Dr. Wechsler, that the cerebellum may be included in the course of the fibers conveying deep sensibilities to the cortex, introduces a new and unusual element into the consideration of the problem.

It is, of course, well understood that the cerebellum receives a large number of proprioceptive impulses over the inferior cerebellar peduncle, but that the fibers carrying these sense qualities may reach the cerebral hemisphere by a detour through the cerebellum, including the inferior and superior peduncles, on their way to the thalamus and, eventually, by one of the thalamic peduncles to the cerebral cortex is a new conception.

I was unable to gain a definite conception of the situation presented by the cross sections of the medulla. However, from the fleeting glimpses obtained, it seems that the upper levels of the medulla did not show any involvement in the region of the mesial fillet. This problem is one which must be settled by careful investigation of the pathologic material and is somewhat apart from the fundamental quarrel which I have with those who seem, from my point of view, to confuse astereognosis with stereoanesthesia.

It seems to me defensible to reserve the term astereognosis for disturbances developing as a result of interference with cortical synthesis and the term stereoanesthesia for similar phenomena which are dependent on disturbances in infracortical regions. As I have said on a number of occasions before this society, it seems worth while to maintain a differentiation, fundamental in character, between disturbance in the ability to synthesize relatively normal primary sense qualities into the appreciation and recognition of objects, and failure to recognize objects by palpation when the primary sense qualities are so defective as to provide insufficient data for the synthesizing activities of the cortex. I know that it is usual to find some defects in the primary sense qualities in patients presenting the syndrome of cortical astereognosis resulting from a lesion in the parietal lobe, but I maintain that certain patients with only minor blunting of their primary sense qualities are unable, as a result of parietal lesions, to synthesize these relatively normal primary sense qualities into the conception of form and the recognition of an object without the aid of the special senses—a condition which has usually been recognized by the term astereognosis. On the other hand, patients may show gross defects in the primary sense qualities and, by reason of these defects, be unable to recognize objects by palpation.

The primary sense quality which is most frequently affected, and by its destruction leads to inability to recognize form, is that concerned with the sense of movement in the hand, the appreciation of the amount of tension brought about by changing postures in the joints, ligaments and muscles connected with the fingers. When the sense of movement is lost there frequently is inability to recognize the

form of objects. The form of an object, however, may fail of recognition by reason of other disturbances in the primary sense qualities. A lesion in the brachial plexus or in a peripheral nerve sufficient to produce superficial anesthesia in the skin of the hand is capable, of course, of preventing the patient from recognizing the form of an object and its identity when placed in the anesthetic hand. This has also been referred to as astereognosis—I believe incorrectly. If this situation were carried to its logical conclusion, one could say that a patient who had no skin and no sensory receptors, being incapable of receiving any stimulation from the surface and of recognizing objects, was therefore suffering from astereognosis. To carry the comparison to its absurd conclusion, if the patient had lost his hand or his arm, he would be unable to recognize objects with the hand, and therefore he might even then be said to be suffering from astereognosis.

This situation, the loss of recognition of objects without the aid of vision, depends on two distinct conditions: one in which the ability to recognize objects is destroyed because the primary sense qualities are so altered that the cortex has no longer the proper building stones out of which to construct the concept of form, the recognition of the object and the application of the name to the object, and the other in which these primary building blocks are present in a relatively unaltered form but the patient is still unable to construct from these relatively normal primary sense qualities the concept of form, the recognition of the object and the application of the name of the object—a disturbance which is essentially astereognosis. The former condition, characterized by inability to recognize objects because of defective primary sense qualities, should, it seems to me, be termed stereoanesthesia.

A fundamental mistake which is frequently made is the failure to recognize the difference between the sense of position, with inability to identify a posture, and the appreciation of movement. I believe that the appreciation of movement, depending on changes in the amount of tension in the muscles, joints and tendons, is a primary sense quality and does not depend on any complex comparison of remotely preceding impressions. The sense of posture and its recognition of position of the fingers or segments of the limbs constitute a synthetic, cortical or gnostic type of sensibility. The recognition of posture is a much more complex process than the recognition of a fluid change in position produced by movement. The direction and knowledge of the actual state of movement are the only things under test in the sense of movement, whereas in the appreciation of a posture one is concerned with the ability to compare a complex integration of a large number of sensory impressions dependent on the tensions in muscles, ligaments, cartilages and other structures, which spells a current posture, with past similar or dissimilar sensory impressions which have been built into the concept and recognition of posture in the organization of the body scheme and its image in the cortex.

It is interesting that Dr. Weinstein and Dr. Wechsler suggest the cerebellum as a pathway for these various sensory impressions, in view of the fact that a former controversy in regard to astereognosis was raised at a meeting of the American Neurological Association, in which Dr. Cushing attributed astereognosis to a cerebellar tumor. The patient in this case was seen by Dr. Kennedy, who concluded that the cerebellar tumor was pressing on the medullary nuclei and was therefore interfering with the inflow of the primary sense qualities and thus producing inability to recognize the object held in the hand. Again this evening, the possibility is being entertained that a lesion of the cerebellum may be productive of astereognosis. This is so new a suggestion to me that I am in doubt as how to evaluate it. The only comment I can make is that in my past experience with tumors and massive destructions of the cerebellum I have never, so far as I can remember, seen any condition like this, in which astereognosis was attributable to gross lesion of the cerebellum.

Dr. Louis Hausman, New York: I was much interested in the presentation by Dr. Weinstein and Dr. Wechsler, but regret that I must dissent from their point of view, for I believe that a simple clinical syndrome is being made complex and difficult. The astereognosis and sensory dissociation which they describe can be produced by lesions at various levels of the nervous system. It occurs with segmental lesions involving the mesial division of the dorsal spinal roots; for that reason, astereognosis may be seen in cases of cervical tabes. In this condition, as is well known, the mesial division of the dorsal root is implicated, but the lateral division, containing the fibers for pain and temperature sense, is spared. Impairment of the dorsal columns of the spinal cord will produce the same type of defect. I am not certain that the authors have proved that the dorsal columns in the upper cervical segments were not involved. A lesion at this site can produce astereognosis, with no impairment of the senses of pain, touch or temperature. The same clinical picture occurs with involvement of the nuclei gracilis and cuneatus, in which the dorsal columns terminate. It also occurs with lesions of the mesial fillet as it passes through the posterior, middle and anterior portions of the hindbrain and the midbrain, and also with lesions of the ventrolateral nucleus of the thalamus and of the parietal cortex.

The point I wish to emphasize is that astereognosis, due to impairment of joint position sense, may occur in association with segmental as well as supra-segmental lesions, anywhere in the path from the mesial division of the dorsal roots to the parietal cortex. The level of the lesion is then determined by concomitant symptoms referable to the particular region. It is incorrect, therefore, to state that this syndrome is characteristic of lesions of the parietal lobe only, for it may occur with lesions at various levels of the nervous system, as I have already indicated.

The authors pointed out in their lantern slides that the mesial fillet was not involved, or rather showed no degeneration. However, this does not rule out the possibility that the dorsal columns themselves may be degenerated, and thus be responsible for the sensory syndrome described.

Dr. Tracy J. Putnam, New York: I find it hard to feel strongly about the proper use of the term "astereognosis." There is something to be said for Dr. Riley's point of view; one ordinarily does not discuss loss of stereoscopic vision, for example, on the basis of cases in which one eye is lost. The only point I should like to question is whether any stain for myelin sheaths is wholly adequate to demonstrate the absence of active fibers. Of course, when one demonstrates fibers with a myelin stain they are present, but one has evidence in many disease processes that functioning fibers may be free from myelin.

Dr. Israel S. Wechsler, New York: This case was presented for two reasons: First, it is not common clinically to see this type of sensory disturbance in cases of lesions of the posterior fossa. One ascribes this kind of sensory loss to a lesion of the parietal cortex and is right nine times out of ten. As a fact, cases such as we reported tonight are sufficiently rare to be worthy of record. When we first saw the patient, it was the impression that she had a tumor of the parietal lobe. It was only after careful neurologic examination and air studies that we made the diagnosis of a lesion of the posterior fossa and decided on exploration. It will be recalled that the patient did not have choked disks for more than a year after the onset of the illness, and that it was the nystagmus and the paralysis of the external rectus muscle which pointed to a lesion of the posterior fossa.

The other reason that we presented the case is the one pointed out by Dr. Riley. The same perplexities which confront him also bother me. The question is primarily one of definition. The problem has repeatedly been discussed in the

literature, and the suggestion has been made that one use astereosymbolia or agnosia instead of astereognosis in cases of so-called pure cortical lesions. The question is: Can one have astereognosis without loss of any of the primary sensory modalities? Most observers think that in cortical astereognosis the position and the discrimination sense are lost at the same time, while touch, vibration, pain and temperature sensations are retained. Is this always true? Obviously, there is astereognosis when touch, pain and temperature sensations are lost, for the reason that the patient cannot feel anything. To say there is astereognosis when there is involvement of the posterior roots is true, but it is also begging the question. In that case there is impairment of every form of sensation, and to rob one of all the primary sense modalities is to make impossible any recognition of objects. It is only as one ascends in the neuraxis that one finds the pathways for conduction of various forms of sensation diverging. This dissociation, which is so characteristic of intramedullary disease, becomes increasingly distinct the higher one ascends. In the cortex there are differences not only in modalities but also in shades. It becomes a question of contrasts, comparisons, nuances, judgment. What must be agreed on is whether the term astereognosis is a generic one, in which case it can have no localizing value in itself, or whether it can have a specific connotation. My opinion, and in this I agree with Dr. Riley, is that it would be well not to use the term indiscriminately and that it should be so defined as to apply to cortical and subcortical lesions—this, whether there is or is not loss of position and discrimination sense. When there is astereognosis due to a lesion at a lower level, the additional sensory impairment and the presence of concomitant signs will serve to localize the lesion.

Dr. Louis Hausman, New York: Dr. Wechsler has misinterpreted my reference to segmental lesions. When I referred to the occurrence of astereognosis in cases of cervical tabes, I did not think it necessary to point out that in these cases the mesial division of the dorsal root is involved and that the lateral division escapes, sparing pain and temperature sensations. Such a lesion would give the picture of astereognosis which could not be differentiated per se from that due to a lesion of the parietal lobe.

Dr. E. D. Friedman, New York: I have had occasion to discuss this question before the Section before, and I do not wish to enter into a long defense of my thesis, which is in accord with that of Dr. Hausman, and to the support of which I can bring the august name of Strümpell. In one of his late papers, Strümpell stated that the concept of astereognosis as postulated by Wernicke (without loss of some of the primary sensations) was untenable, and that if neurologists would take the trouble to examine carefully the position and joint sense in cases in which there is astereognosis they would find impairment of this sensory modality. The proprioceptive sense is disturbed, and without that disturbance one cannot have astereognosis. I hesitate to make a dogmatic statement, but I suggest that the subject be reviewed by those who differ from this point of view. It might be possible finally to come to some agreement on the significance of these symptoms and the name one should give them. As astereognosis is understood at present, however, the basis is a disturbance in the primary position and joint mobility senses.

Dr. Edwin A. Weinstein, New York: In answer to Dr. Putnam's point: I agree that the myelin sheath stain is not entirely adequate. I did not mean to indicate that conduction was entirely interrupted. On the contrary, I stressed as clinical proof of function that the vibratory sensation was intact.

In answer to Dr. Hausman: It is not simply a matter of destruction of the posterior column or the medial lemniscus at any level. In a recent review,

Bender and I found that in cases of lesions of the spinal cord in which deep sensibility in the lower extremities was affected and dissociation occurred vibratory sense suffered first. When dissociation was present in the upper limbs, position sense was the more severely involved. This indicates that it is not simply a matter of vulnerability of the posterior columns anywhere in their course.

In reply to Dr. Riley: The disturbance is just as true and critical an astereognosis as occurs with cortical lesions and is accompanied by impairment of position sense and two point discrimination. As Dr. Friedman pointed out, astereognosis without involvement of either modality must be rare. The fact that touch and vibratory sensations were intact removes the objection that the astereognosis was of necessity caused by a defect in primary sense modalities.

As for the statement that this sensory picture can be produced at any level of the neuraxis, I can conceive of it only as occurring with lesions around the foramen magnum and in the cortex.

It was the accident that a lesion occurred where cerebellar and lemniscus fibers diverge, and do not join again until the cortex is reached, that enabled this picture to be produced.

Obituaries

WILLIAM GIBSON SPILLER, M.D.
1863-1940

Dr. William Gibson Spiller was born in Baltimore, Sept. 13, 1863, the son of Robert Miles Spiller, of King William County, Va., and Anne Augusta (Maltby) Spiller. His education, preliminary to the study of medicine, was obtained at the Cheltenham Military Academy, near Philadelphia, and was completed at the University of Pennsylvania School of Medicine, from which institution he graduated in 1892, with the degree of Doctor of Medicine.

Following his graduation, Spiller went to Europe and studied under the tutelage of experts in cardiology and nervous diseases in London, Berlin, Paris and Vienna. Eventually he specialized in neurology and was the close student of Obersteiner, Edinger, Marburg, Dejerine and Gowers. Returning to America in 1896, he came to Philadelphia and associated in neurologic work with Dr. Charles K. Mills at the Philadelphia Polyclinic Hospital, where adjustment to his new surroundings was rapid, and in 1901 he became head of the department of neurology at that institution, when Dr. Mills assumed the chair of nervous diseases at the University of Pennsylvania School of Medicine. In 1902 Spiller was appointed clinical professor of nervous diseases in the Woman's Medical College of Pennsylvania and served in that capacity until 1925. In 1903 he was made professor of neuropathology and associate professor of neurology in the department of medicine of the University of Pennsylvania, occupying these positions until 1915, when, after the resignation of Dr. Charles K. Mills, he was given professorial charge of the department of neurology at his alma mater, and retained that office until 1932, when he was created professor emeritus. From the University of Pennsylvania, in 1935, he received the degree of Doctor of Science, and in the same year, by Lafayette College, he was honored with the degree of Doctor of Laws.

On the day of Dr. Spiller's first appearance at the old Polyclinic Hospital, in Philadelphia, his ability as a teacher was evident. He had been thoroughly grounded in the basic principles of nervous diseases, and during his stay in Europe had acquired a wide knowledge not only of the ordinary symptoms but also of the more subtle and less well known signs of disease; his method of transmitting his knowledge was stimulating. Discussions between him and Dr. Mills in the presence of the Polyclinic students were always productive of ideas that would

never have come to light had it not been for the differences in the methods of approach of the two men.

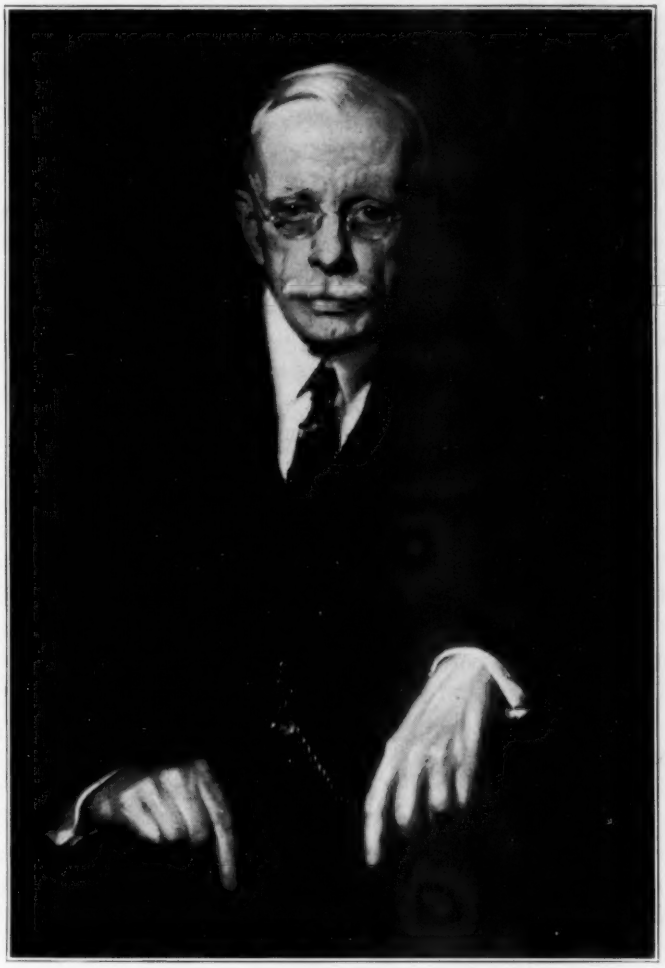
Later, Spiller became one of the chiefs at the Philadelphia General Hospital and a member of the coterie consisting of Mills, Dercum, Lloyd and Burr, who, with their assistants and "hangers-on," would spend hours of an afternoon discussing the diagnoses of patients in the wards of that great institution. Always modest, Spiller would quietly sit and listen to the thoughtful remarks of the older members of the staff until the question would be propounded: "Well, Spiller, what do you think of it?" . . . Dr. Spiller would then give his analysis of the afternoon's work, at once enlightening and diagnostically final.

For the undergraduate students much of Spiller's thinking was, at first, expressed in language too scientific for them to grasp, but later and closer contacts with the student body brought to him the recognition of his real mission, namely, to give the learners what they needed—a knowledge of the general subject of neurology which they could elaborate at their convenience and pleasure. As the years went on and he advanced from one teaching position to another, climaxing his career as professor of neurology in the University of Pennsylvania School of Medicine, his presentations became outstanding events among undergraduate and graduate bodies.

His work in the outpatient neurologic service of the University of Pennsylvania was the last word in meticulous study. His assistants in this work included men who are today members of the American Neurological Association—McConnell, Cadwalader, Wilson, Hadden, Winkelman, Ludlum, Ornsteen, Thompson, McIver, Camp (Ann Arbor, Mich.), Fay, the late Theodore Weisenburg and others who recognized Spiller's superior talents and profited by association with him. He was critical of histories, of lists of symptoms, of deductions, always to the technical advantage of the one criticized. In the busy years from 1896 to 1910, Spiller conducted research in the William Pepper Laboratory of the University of Pennsylvania. By his careful study of gross pathologic specimens and by microscopic examinations, he verified or discounted many of the diagnoses of neurologic conditions made by his colleagues and himself.

The widespread clinical work and the results of his investigation of an enormous collection of specimens furnished the material for his contributions to medical literature, which were many and ran the gamut from purely clinical reports through pathologic studies to the eventual consideration of real neurologic problems from all standpoints. He regarded his joint papers with Dr. Charles H. Frazier, in which were discussed the operations on the sensory root of the fifth nerve, as his most important practical offering. Others might take into account his work with Posey on "The Eye and the Nervous System," or the presi-

dential address delivered by him to the American Neurological Association, entitled "The Importance in Clinical Diagnosis of Paralysis of Associated Movement of the Eyeballs (*Blicklähmung*), Especially the Upward and Downward Associated Movements." His articles on



WILLIAM GIBSON SPILLER, M.D.
1863-1940

chordotomy showed the keen Spillerian research instinct for things that either would perfect him in his knowledge of neurology or would give him various means for relieving those suffering from nervous diseases.

With all the interest he had in clinical neurology and in the therapeutics of nervous diseases, Spiller for years absolutely refused to enter

the private practice of neurology. Not until 1910 did his friends eventually impress on him the importance of his entering the field of consultation; after he did so, when people commenced to depend on him, when he began to realize what he could do, he failed to exhibit any of the pleasurable reactions that most practitioners derive from service successfully rendered. Many times he would express himself as being uninterested in the practice of his art and wished for uninterrupted study.

His offices were always quiet places, somewhat bare of any decoration, like the room of an ascetic. After writing the history of his patient and beginning his general examination, he seemed to lose all sense of anything other than the symptomatology he was looking for, the diagnosis he hoped to make and the treatment he expected to prescribe. The most insignificant feature was thoroughly analyzed; the common physical signs were never neglected. Some persons regarded him as a cold scientist; but frequently, when telling patients or their friends of the hopelessness of a situation, Spiller showed evidence of great depth of feeling, almost an emotional upset. To him, always, a patient was something to be studied, a pathologic condition to be combated, a human life to be saved—the last a problematic thing. Despite his appearance of lack of heartfelt interest and his dolefulness in the sick room, he was a dependable consultant, a giver of sound advice.

By many of his associates and students Spiller's methods relative to patients and other scientific matters were often regarded as selfish. This was a great misunderstanding of the man and a sad error of judgment on the part of the critics. At all times Spiller was companionable. The apparent "one manness" was without doubt the result of his early training abroad, for not infrequently he spoke of the thoroughness with which Obersteiner, Marburg and others with whom he had studied would go over a patient, and the lack of this feature among American neurologists annoyed him. For a time he had little regard for much of the clinical or literary work done by the neurologists of America, but increasing familiarity with his friends of neurologic bent and the ripening of opinions, spoken and written by them, gradually overcame his prejudice, but did not change his methods. Like his teachers, he was constantly looking for new symptoms or the modifications of recognized ones. In this way he felt he would be able to clarify little known pathology, or such attention to detail would give him greater understanding of the abnormal features of his postmortem specimens.

Spiller's memory was uncanny, but this mnemonic characteristic did not relate alone to professional knowledge. For a time he was editor of the *Journal of Nervous and Mental Diseases*, and, with scientific literature as his daily pabulum, he became thoroughly acquainted with

neurologic materials, which he divided among students and co-workers. If the question was raised as to any article on nervous disease, Spiller usually had the answer and would recite the title of the book or journal, the date of its publication, the name of the author and almost the page on which certain facts could be found. Quite evident was his familiarity with current novels; Shakespeare seemed to be a close friend, and he could recite lines from the plays of that poet, without rehearsal and pertinently to the occasion.

Spiller's friendships were close ones. He enjoyed meeting those who were interested in the same things as himself, and his attendance at local and national scientific organizations was always expected. He was a member of the American Medical Association; of the American Neurological Association, of which he was president in 1906; of the Philadelphia Neurological Society, of which he was a chairman; the American Association of Neuropathologists, and the American Association for Research in Nervous and Mental Diseases. By foreign societies he was honored with corresponding membership in the Gesellschaft deutscher Nervenärtze; the Société de Neurologie de Paris; Verein für Psychiatrie und Neurologie, Vienna, and the Société Estonienne de Neurologie. For many years he was honorary consultant in neurology at the Philadelphia General Hospital.

Spiller was essentially a family man. He was married on Jan. 3, 1888, to Miss Helen C. Newbold, daughter of Rev. William Allibone and Martha Smith (Baily) Newbold. Four children resulted from this marriage: Mrs. Randolph G. Adams, of Ann Arbor, Mich.; Prof. Robert Ernest Spiller, of Swarthmore College, Swarthmore, Pa.; William Raymond Spiller, chief engineer, Harris-Seybold-Potter Co., of Dayton, Ohio; Donald P. Spiller, engineer, American Telephone & Telegraph Co., Philadelphia. In the education of his daughter and his sons he was not only deeply interested but anxious for the best schools, where each could obtain the most satisfactory results in their chosen lines. Illness among them was rare, but when it occurred he was the father, not a physician.

In the last few years of his teaching life, Spiller recognized the necessity for catering to his physical makeup and considerably contracted his activities. His resignation from the professorial chair at the University of Pennsylvania was a great sorrow to him. Following the relinquishing of this duty the days were filled with pain and advancing physical infirmity. His mind, however, was clear. He was fond of the visits of his associates and acquaintances; he enjoyed professional gossip and the news of his coterie of friends. On March 18, 1940, a great neurologic light was extinguished with his death; a unique personality passed on; a good companion vanished.

J. W. McConnell, M.D.

JOSHUA ROSETT, M.D.
1875-1940

Dr. Joshua Rosett died in Yucatan on April 1, 1940. He was on his way home from Mexico, whither he had gone to study Mayan ruins and Indian culture, when he was stricken with a gastric hemorrhage from which he failed to rally.

Dr. Rosett was born in Russia in 1875; he came to this country as a young man, obtained his medical degree in Baltimore in 1903, practiced general medicine there for many years and held a position as officer in the department of health of that city. During the World War he served in Siberia with the American Army. On his return he settled in New York and soon became associated with the department of neurology of the College of Physicians and Surgeons. He was appointed assistant professor of neurology in 1920 and professor in 1935. He was a member of practically all the local and national neurologic societies.

Although Dr. Rosett held some clinical postions and practiced neurology from time to time, he devoted himself essentially to research. He contributed valuable papers on myotonia, sleep and epilepsy. His studies on hyperpnea were original and anticipated those of Foerster. His outstanding and most permanent work was done on the anatomy of the brain, more particularly the intercortical systems, the occipitofrontal association tract and other long cerebral pathways. He showed most originality in what he called "exploding" the brain for the purposes of study of the long association systems, and in preserving brain material. He left behind innumerable specimens of the brain, beautifully illustrating for didactic purposes the various cerebral structures.

Dr. Rosett was in many ways gifted with original talent. He was very ingenious in devising new methods in anatomic research. He was also interested in plants, many of which he stained and preserved in remarkable lifelike fashion. Like many genuine scientists, he was also somewhat of a poet and an artist. Indeed he possessed considerable talent as a writer. Aside from his scientific contributions, which have literary excellence, he wrote plays, short stories and a philosophic-sociologic novel.

Like most men of worth, Joshua Rosett possessed a conflicting, and in some ways contradictory, personality. He combined within himself originality, insight and even wisdom with a curious and sometimes tantalizing naïveté. Yet he knew life well, had a true social sense and saw through the hypocrisy which attends many human relations. Withal he had a real capacity for friendship.

There is a certain finality about death which mocks many of the activities that men take seriously during life. Joshua Rosett knew this. He took neither himself nor others very seriously. He saw through much of the sham and the wickedness which passes for civilization and detested with deep emotion the revival of barbarity which dominates certain peoples and nations. Although this did not darken his life, it served to take some of the joys out of it. He found most contentment in his manifold activities, especially in his scientific work. Much of this has the mark of permanent worth.

I. S. WECHSLER, M.D.

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

At the meeting held on May 17 to 19, 1940, at Cincinnati, the following candidates were granted certificates:

Neurology.—On Record: Leizer E. Grimberg, New York.

By Examination: * David Armitage Boyd Jr., Indianapolis; Joseph P. Evans, Cincinnati; Robert Lee Glass, Indianapolis; Robert W. Graves, Durham, N. C.; * Herbert E. Heim, Harrisburg, Pa.; * Leo Maletz, Hathorne, Mass.; Augustus S. Rose, Boston; John T. Shea, Foxboro, Mass.; William Axel Smith, Atlanta, Ga.; Theodore J. C. von Storch, Boston.

Psychiatry.—On Record: Felix M. Adams, Vinita, Okla.; Serge Androp, Catonsville, Md.; † Percival Bailey, Chicago; George F. Brewster, Northport, N. Y.; Sarah R. Kelman, New York; Charles I. Lambert, New York; Bernard Thomas McGhie, Toronto, Canada; Anna E. Parker, Boston; Carl W. Sawyer, Marion, Ohio.

By Examination: Walter H. Baer, Peoria, Ill.; Crawford N. Baganz, Lyons, N. J.; William Y. Baker, Seattle; Samuel Cohen, Philadelphia; Anna C. D. Colomb, Philadelphia; Charles B. Congdon, Chicago; Arthur M. Doyle, Boston; John W. Evans, Portland, Ore.; Albert H. Fechner, Lincoln, Neb.; Maxwell Gitelson, Chicago; Paul A. Gliebe, San Francisco; Hyman H. Goldstein, Chicago; John H. Greist, Indianapolis; Granville L. Jones, Marlboro, N. J.; Ronald H. Kettle, Norwich, Conn.; Morris Kleinerman, Washington, D. C.; Maurice Levine, Cincinnati; Arthur Lindenfeld, Allentown, Pa.; Nathan Malamud, Ann Arbor, Mich.; Benjamin Margulois, Palmer, Mass.; Donald A. R. Morrison, Oconomowoc, Wis.; John M. Murray, Boston; Mollie E. Orloff, Norristown, Pa.; Michael J. Pescor, Fort Worth, Texas; Magnus C. Petersen, Willmar, Minn.; Philip Piker, Cincinnati; Saul K. Pollack, Milwaukee; Conrad O. Ranger, Concord, N. H.; Leon Reznikoff, Secaucus, N. J.; Harry N. Roback, Medical Lake, Wash.; John A. Rose, Philadelphia; Ralph Rossen, Hastings, Minn.; Louis B. Shapiro, Elgin, Ill.; Alfred W. Snedeker, Staten Island, N. Y.; Israel R. Sonenthal, Chicago; Olga E. Steinecke, Taunton, Mass.; Henry A. Tadgell, Wrentham, Mass.; † Walter A. Thompson, Orangeburg, N. Y.; Bernard O. Wise, Howard, R. I.; Samuel A. Zeritsky, Philadelphia.

Psychiatry and Neurology.—On Record: Charles Frederick Becker, Camden, N. J.; Bernhard Berliner, San Francisco; DeWitt Clinton Burkes, Portland, Ore.; Henry Milligan Chandler, Orangeburg, N. Y.; Samuel N. Clark, Jacksonville, Ill.; Wladimir Eliasberg, New York; Joseph H. Globus, New York; William J. Hammond, Westwood, Mass.; Leslie B. Hohman, Baltimore; Michael Kasak, Wauwatosa, Wis.; James Lewald, Laurel, Md.; Lawson C. Lowrey, New York; Louis A. Lurie, Cincinnati; Hermon S. Major, Kansas City, Mo.; Hyman A. Osserman, New York; Joseph H. Toomey, Bronx, N. Y.; L. Maude Warren, Waverley, Mass.; James J. Waygood, Philadelphia; Israel S. Wechsler, New York; Herbert C. Woolley, Philadelphia.

* This award is complementary to one previously granted in psychiatry.
† This award is complementary to one previously granted in neurology.

By Examination: Alex J. Arieff, Chicago; A. B. Baker, Minneapolis; Gilbert M. Beck, Buffalo; Basil T. Bennett Jr., Boston; Nathaniel J. Berkwitz, Minneapolis; Benjamin Boshes, Chicago; Harold R. Carter, Washington, D. C.; Thomas H. Cheavens, Dallas, Texas; Owen C. Clark, Oconomowoc, Wis.; Edwin M. Cole, Boston; L. McKendree Eaton, Rochester, Minn.; James Greenwood Jr., Houston, Texas; Bernard A. Hirschfield, Trenton, N. J.; William K. Keller, Louisville, Ky.; Jennie D. Klein, Buffalo; Norman A. Levy, Chicago; John J. Madden, Chicago; Franklin O. Meister, Madison, Wis.; Henry S. Millett, Kansas City, Mo.; Dwight M. Palmer, Columbus, Ohio; Harry M. Salzer, Cincinnati; Maurice A. Schiller, Chicago; Robert S. Schwab, Boston; Laurence D. Trevett, Georgetown, Mass.; Louis L. Tureen, St. Louis; Richard H. Young, Omaha; Alexander Wolf, New York.

OPPORTUNITIES FOR FELLOWSHIPS

A limited number of fellowships have been provided by the Commonwealth Fund and other sources of training in extramural, especially child, psychiatry. These fellowships are to be administered by the National Committee for Mental Hygiene, through which fellows are to be assigned for one or two years to a selected child guidance clinic, the term and plan of the fellowship to be determined by the peculiar needs of the fellows. Candidates for fellowship award should have had at least two years of psychiatric training in an approved hospital for persons with mental disease, in addition to other qualities fitting them for extramural service. These fellowships come in response to a definite paucity of personnel in this field. Accordingly, other conditions, as to age, sex and marital status, must be governed by individual cases and by the nature of current demand. Requests for further information about these fellowships, and applications therefor, should be addressed to Dr. Milton E. Kirkpatrick, the National Committee for Mental Hygiene, Room 822, 50 West Fiftieth Street, New York.

THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

The first examination for certification of candidates by the American Board of Neurological Surgery, Inc., will be held at the Neurologic Institute at the University of Illinois, 804 South Wood St., Chicago, Oct. 18 and 19, 1940. Application forms and copies of the charter and by-laws may be obtained from the secretary, Dr. R. Glen Spurling, 404 Brown Building, Louisville, Ky.

Abstracts from Current Literature

Anatomy and Embryology

VENTRAL HORN CELLS AND POLYDACTYLY IN MICE. YÜ-CH'ÜAN TSANG, J. Comp. Neurol. **70**:1 (Feb.) 1939.

Tsang studied the multipolar cells of the ventral horn at the lumbosacral level of the spinal cord in 19 polydactylous mice and in 6 normal mice. The musculature of the foot is innervated by the motor nerves, the cells of origin of which are in the retrodorsolateral column. The extent of this cell column was determined, and the size and number of nerve cells on each side were compared. In 10 of the polydactylous mice Tsang recognized hypertrophy of the retrodorsolateral column on the side of the duplicate digit. He concluded that polydactyly in the mice studied was the consequence of hypertrophy of the retrodorsolateral cell column.

FRASER, Philadelphia.

THE ORIGIN OF THE CORPUS CALLOSUM AND THE FATE OF THE STRUCTURES RELATED TO IT. A. A. ABBIE, J. Comp. Neurol. **70**:9 (Feb.) 1939.

Abbie studied the evolution of the corpus callosum in Ornithorhynchus, Tachyglossus, Perameles, Trichosurus, Erinaceus, Cynopterus, Rattus, Felis and Macacus. In monotremes and marsupials there are two commissures crossing in the lamina terminalis, one coming from the hippocampus and the other from the remainder of the cerebral hemisphere. The fibers of the corpus callosum do not traverse the preexisting hippocampal commissure, but make a new pathway by passing directly through the subiculum, dorsal to the hippocampus and across the top of the lamina terminalis. The septum pellucidum is formed by the drawing up of the anterior part of the lamina terminalis within the concavity of the frontal callosal arc. The cavum appears when the tension from the expanding arc produces condensation of the septum into two laminas, with a cavity between them.

ADDISON, Philadelphia.

THE REGENERATION OF END-ARTERIES IN THE OPOSSUM BRAIN. ERNST SCHARRER, J. Comp. Neurol. **70**:69 (Feb.) 1939.

The opossum is the only mammal on record to have exclusively end arteries in the brain. Scharrer operated on 15 adult opossums by excising a piece of cortex and implanting in its place a piece of cortex from an opossum brain which had been fixed in formaldehyde and rinsed in sterile solution of sodium chloride. The wound was then closed, and the animals were allowed to survive for from two to fifty-six days. The blood vessels of the brain were injected with a solution of india ink and gelatin. Increase in vascularity adjoining the lesion was not observed. There was marked dilatation of the capillaries around the lesion. Capillaries which had been cut showed regeneration, but anastomoses were never seen.

ADDISON, Philadelphia.

THE DIFFERENTIATION BETWEEN NEUROGLIA AND CONNECTIVE TISSUE SHEATH IN THE COCKROACH (PERIPLANETA AMERICANA). BERTA C. J. SCHARRER, J. Comp. Neurol. **70**:77 (Feb.) 1939.

Serial sections through the cerebral ganglion of Periplaneta americana were studied after many varieties of fixations and stains. Two types of non-nervous tissue were distinguished topographically. The entire ganglion was covered with a connective tissue sheath, called the perilemma, which consists of a layer of cells, the perineurium, covered by a distinct membrane, the neural lamella. These

cells did not enter the central nervous system. The neuroglial elements occurred in the central nervous system, where they formed strands of varying thickness between the peripheral groups of nerve cells and the central fiber mass.

FRASER, Philadelphia.

FIBER RATIOS IN REGENERATING NERVES: II. THE STATUS OF REGROWTH OF THE SCIATIC AND NERVES TO THE GASTROCNEMIUS IN MACACUS 3 MONTHS AFTER SECTION. H. A. DAVENPORT, HERMAN CHOR and D. A. CLEVELAND, J. Comp. Neurol. **70**:153 (Feb.) 1939.

This study is part of a program of investigation concerned with the effect of therapeutic procedures on the regeneration of denervated muscle. Seven monkeys were used. The sciatic nerve was cut on one side at the level of the great trochanter of the femur and then sutured immediately by end to end anastomosis. After three months blocks of tissue were taken from three regions: (1) the healed lesions, together with about 1 cm. each of the proximal and distal stumps; (2) 1 cm. of normal nerve from the opposite side, and (3) the bundle of nerves entering the gastrocnemius muscles, from both the normal side and the side of operation. The tissue was fixed in Bouin's fluid for three days. Pieces were then taken from above and below the site of suture and from both the regenerating and the normal nerve as they enter the gastrocnemius muscle, as well as from the normal sciatic nerve. These were stained with osmium tetroxide; others were stained on the slide by a silver method.

The number of myelinated fibers in the sciatic nerve proximal to the site of operation averaged 34,000. In the distal stump the number of fibers which had regrown and acquired sufficient myelin to react to osmium tetroxide averaged 21,600, and the number shown with the silver stain averaged 64,000. The total number of fibers in the normal sciatic was approximately 1,000,000. The authors compare these results of study of regrowth of the sciatic nerve with those previously published by two of them (Davenport and Chor) in which regeneration had been allowed to progress for six months. After this interval 84,000 fibers were present.

ADDISON, Philadelphia.

THE TRACTUS TEGMENTI MEDIALIS AND ITS CONNECTION WITH THE INFERIOR OLIVE IN THE CAT. TEIZO OGAWA, J. Comp. Neurol. **70**:181 (April) 1939.

Ogawa studied the tractus tegmenti medialis in 14 cats. Lesions were produced by the stereotaxic apparatus in the mesencephalic tegmentum, or in the region of transition between it and the hypothalamus. The medial tegmental tract consists of numerous fine myelinated fibers which extend from the level of Forel's field to the homolateral inferior olive. The tract appears to arise in the nucleus of Darkschewitsch, the nucleus interstitialis of Cajal and the nucleus of Forel's field. It has not been demonstrated in man.

ADDISON, Philadelphia.

THE LATERAL-LINE ORGANS OF LIVING AMPHIBIAN LARVAE WITH SPECIAL REFERENCE TO ORANGE COLORED GRANULES OF THE SENSORY CELLS. SULLIVAN G. BEDELL, J. Comp. Neurol. **70**:231 (April) 1939.

The lateral-line organs were observed in the tail fin of the tadpoles of Rana clamitans while under anesthesia induced with chlorobutanol. In freshly caught tadpoles, one to nine clumps of prominent, clearly defined orange granules were seen in each lateral-line organ. These granules were of protein nature. The granules disappeared completely within four to six weeks in animals kept in the laboratory. When these animals were placed in ideal conditions the granules reappeared. Degeneration of the nerve supply to lateral-line organs neither hastened nor retarded the disappearance of the granules.

ADDISON, Philadelphia.

THE INTRAMEDULLARY COURSE OF THE UPPER FIVE CERVICAL DORSAL ROOT FIBERS IN THE RABBIT. JAMES YEE and KENDALL B. CORBIN, J. Comp. Neurol. **70**:297 (April) 1939.

Yee and Corbin studied the intramedullary course of the upper five cervical dorsal roots in 22 rabbits. Ganglia of these roots in various combinations were removed. After intervals of from eight to fifteen days the pons, the medulla and the adjoining portion of the spinal cord were removed. The blocks of tissue were treated by the Marchi procedure. Fibers from the dorsal roots of the first and second cervical nerves descended three segments, and fibers from the dorsal roots of the third to the fifth cervical nerves descended four segments below the level of entrance of the root. In the segment of entry the fibers showed a fourfold distribution: (*a*) the majority passed to the central gray substance in and about the intermediate nucleus of Cajal; (*b*) some passed to the homolateral posterior gray column; (*c*) a few went to the homolateral ventral gray column, and (*d*) a still smaller number crossed in the posterior gray commissure.

ADDISON, Philadelphia.

THE SENSORY INNERVATION OF THE SPINAL ACCESSORY AND TONGUE MUSCULATURE IN THE RABBIT. JAMES YEE, FRANK HARRISON and KENDALL B. CORBIN, J. Comp. Neurol. **70**:305 (April) 1939.

Yee, Harrison and Corbin studied the innervation of the spinal accessory muscles (sternomastoid, cleidomastoid and trapezius) and the muscles of the tongue in 64 rabbits. Various of the upper five cervical dorsal root ganglia were removed unilaterally or in different bilateral combinations. Certain cervical ventral rami were also sectioned in some rabbits. Seven to fifteen days were allowed for degeneration, after which the animals were killed and the representative portions of (1) the hypoglossal nerve and its branches, (2) the spinal accessory nerve and its branches and (3) the various upper five cervical ventral rami were treated by the Marchi technic or with osmium tetroxide. Other rabbits were used for oscillographic studies. In no instance did stimulation of any of the peripheral ends of the upper five cervical ventral rami cause contraction of the spinal accessory or tongue musculature, which indicates that the accessory muscles receive their entire motor supply from the spinal accessory nerve. Twenty-five to 50 per cent of the fibers supplying the accessory muscles were found to be sensory. Oscillographic and degeneration experiments showed that the accessory muscles received the fibers carrying muscle sense from the third and fourth cervical dorsal root ganglia, through the respective cervical ventral rami, branches of which anastomose extraspinally with the spinal accessory nerve. The ganglia of the dorsal root of the first cervical segment were a partial source of fibers carrying proprioceptive impulses from the tongue musculature.

ADDISON, Philadelphia.

THE CAPILLARY BEDS OF THE PARAVENTRICULAR AND SUPRAOPTIC NUCLEI OF THE HYPOTHALAMUS. KNOX H. FINLEY, J. Comp. Neurol. **71**:1 (Aug.) 1939.

Finley studied in serial sections the brains of monkeys which had been injected with india ink. Rich capillary distribution was seen in the paraventricular and supraoptic nuclei, two nuclei which have special and similar structures. Here the capillaries were more dense than in any other nuclear or cortical region of the central nervous system, except for a nucleus in the floor of the fourth ventricle. The structure of the individual capillary in the paraventricular or in the supraoptic nucleus is not different from that in other parts of the central nervous system. These two nuclei are considered to be receptors which react to physicochemical changes in their rich blood supply, and Finley suggests that the impulses from their nerve cells, which are conducted into the neural portion of the hypophysis, are set up by humoral changes in the blood.

ADDISON, Philadelphia.

THE HYPOGLOSSAL NERVE IN HUMAN EMBRYOS. ANTHONY A. PEARSON. J. Comp. Neurol. **71**:21 (Aug.) 1939.

Pearson presents the second in a series of studies on the development and analysis of the cranial nerve components in human embryos. Six human embryos, between 17 and 46 mm. in crown-rump length, were available. In the 25 mm. embryo the hypoglossal nucleus showed as a prolongation of the cervical ventral gray column into the medulla. At the 45 mm. stage the cell column of the hypoglossal nerve showed division into a dorsal and a ventral cell column. The cephalic end of the dorsal column was divided into a medial and a lateral part. The twelfth nerve was found to have communicating branches which connected it with the first and second cervical nerves, the superior cervical sympathetic ganglion or the sympathetic trunk, the carotid plexus, the lingual nerve and sometimes with the hypoglossal nerve of the other side. Pearson found no evidence that either Roller's nucleus or the nucleus intercalatus contributed to the hypoglossal nerve.

FRASER, Philadelphia.

THE NUCLEAR CONFIGURATION OF THE OLFACTORY AND ACCESSORY OLFACTORY FORMATIONS AND OF THE NUCLEUS OLFACTORIUS ANTERIOR OF CERTAIN REPTILES, BIRDS AND MAMMALS. ELIZABETH CAROLINE CROSBY and TRYPHENA HUMPHREY, J. Comp. Neurol. **71**:121 (Aug.) 1939.

Crosby and Humphrey made an extensive study of the nuclear configuration of the olfactory and accessory olfactory formations and of the nucleus olfactorius anterior of a variety of vertebrates as a part of a series of reports on the nuclear configuration and fiber connections of the telencephalon in reptiles, birds and mammals. Serial sections, cut either sagittally or transversely, were available from 6 species of turtles, 4 of snakes, 1 of crocodile, 5 of lizards, 6 of birds and 10 of mammals.

The olfactory bulbs showed a wide range in size and in layer differentiation throughout. Accessory olfactory bulbs were observed in the brains of turtles, lizards, snakes and all mammals studied, except the bat, macaque and man. The major subdivisions of the nucleus olfactorius anterior were present throughout the group, except for the pars externa and the pars posterior. In general, the size of this nucleus was in direct proportion to the degree of development of the bulbar centers and in inverse proportion to the amount of forward specialization of the hemisphere.

FRASER, Philadelphia.

Physiology and Biochemistry

THE MECHANISM OF VISION: XVI. THE FUNCTIONING OF SMALL REMNANTS OF THE VISUAL CORTEX. K. S. LASHLEY, J. Comp. Neurol. **70**:45 (Feb.) 1939.

Lashley's problem has been to determine the smallest remnant of visual cortex which will mediate the discrimination of visual figures. The entire right striate area and large amounts of the left striate area of the visual cortex were destroyed. Estimates are given of the number of nerve cells at successive levels of the visual system. The animals were trained, operated on and, fourteen days after operation, tested for retention of visual images. Complete serial sections through the lateral geniculate nuclei and the cortical lesions were studied. Discrimination of visual figures was observed in animals with not less than 700 normal neurons in the geniculostriate system. This is about one fiftieth of the normal number.

FRASER, Philadelphia.

A REGIONAL VOLUMETRIC STUDY OF THE GRAY AND WHITE MATTER OF THE HUMAN PRENATAL SPINAL CORD. A. M. LASSEK and G. L. RASMUSSEN, J. Comp. Neurol. **70**:137 (Feb.) 1939.

Lassek and Rasmussen studied the regional gray and white substance of the human spinal cord, from a quantitative standpoint, in a series of 19 Negro fetuses

ranging in age from 3.9 to 10 lunar months. The length of the cord and the weight and gross volume were determined after removal of the pia. The cord was then impregnated with silver or with osmium tetroxide. The outlines of the gray and white substances were drawn and the relative cross sectional areas determined by measuring their outlines with a planimeter. Values were adjusted to correspond with true volumes as determined earlier. From the ages of 3.9 to 10 lunar months, the total length of the spinal cord increased 2.8 times, the cervical portion 2.8 times, the thoracic 3 times, the lumbar 2.3 times and the sacral 2.2 times. At all stages the cervical portion averaged 26.2 per cent of the total volume of the spinal cord. The ratio of the length of the spinal cord to the body length gradually changed from 1:2.7 at the fetal age of 3.9 months to 1:3.3 at birth. The ratio of the volume of white substance to that of gray substance gradually increased from 0.8:1 at 3.9 months to 1:1 at 5.3 months and to 1.6:1 at birth. In the series studied, the white substance as a whole increased twice as fast as the gray, and the thoracic region exhibited the most striking changes in growth. At all stages of prenatal development the cervical region had the greatest amount of gray and white substance, followed in order by the thoracic, lumbar and sacral regions.

ADDISON, Philadelphia.

STUDIES IN THE PHYSIOLOGY OF THE EMBRYONIC NERVOUS SYSTEM: II. EXPERIMENTAL EVIDENCE ON THE CONTROVERSY OVER THE REFLEX THEORY IN DEVELOPMENT. ZING YANG KUO, J. Comp. Neurol. **70**:437 (June) 1939.

Kuo offers evidence in the controversy over the reflex theory in development from experimental work on the embryonic nervous systems of the chick and frog. His experiments were devised to study various factors which determine whether a given response of the embryo in a given movement involves only one organ or more than one. Independent movements, spontaneous movements, and movements in response to electrical stimuli were recorded. The responses of the forelimb, hindlimb, tail, eye and beak were observed. The development of somatic motility was divided into ten stages. The percentage of independent movements of each organ increased with age. The percentage of independent movements increased in quieter stages, but dropped again when in the last stage, the stage of hatching, movements became vigorous and violent. Independent reflexes in response to electrical stimuli increased with age, but did not decrease at hatching. In later stages of development independent movements of the beak and eye were more numerous than those of other organs. Kuo found the following factors effective in movements: (1) stage of development; (2) environmental conditions; (3) health conditions of the embryo; (4) position of the embryo; (5) curarization; (6) intensity of stimuli; (7) interval between stimuli; (8) number of repetitions of stimuli; (9) strength and magnitude of the initial movements; (10) activity of body parts in different stages of development, and (11) nature of movements previous to stimulation. Kuo says that his evidence does not lend support to either of the two current reflex theories.

ADDISON, Philadelphia.

THE EFFECTS OF COMBINED RED NUCLEUS AND PYRAMIDAL LESIONS IN CATS. BYRON H. EVANS and W. R. INGRAM, J. Comp. Neurol. **70**:461 (June) 1939.

Evans and Ingram studied the effects of combined lesions of the rubrospinal and the pyramidal system in cats, both as to influence on muscle tone and postural reactions and as to possible mutual compensatory activity. Bilateral lesions in the red nucleus were produced by the stereotaxic instrument. The pyramidal tract was cut with a fine-pointed knife. In 5 cats, lesion of the red nucleus was followed by section of one pyramid; in 4 cats, lesion of the red nucleus was followed by section of both pyramidal tracts, and in 2 cats pyramidal section was followed by

lesion in the red nucleus. In 3 cats only pyramidal section was performed. Observations were made on the following: (1) gait and general posture; (2) righting reactions; (3) visual and contact placing reactions; (4) hopping reactions, and (5) tonus of extensor muscles of the limbs. Partial section of the pyramid gave variable results. In some cases there were increase in extensor tonus and deficiency in the postural reactions in the contralateral limbs, with occasional slight paresis; in other cases these defects were slight except for deficiencies in postural reactions. If the effects of the lesion of the red nucleus had been well overcome before the lesion was made in the pyramidal tract, pyramidal section caused return of hypertonus and dysmetria, with loss of postural reactions in the contralateral limbs and with milder ipsilateral effect. Somewhat similar reemphasis of symptoms occurred when the red nuclei were damaged subsequent to pyramidal section. Compensation occurred in time. Evans and Ingram suggest that both the pyramidal and the rubrospinal system participate in the complex mechanism regulating muscle tonus and economy of movement in cats, and that each may act to compensate to a considerable extent for loss of the other. Their results do not explain how compensation occurred when both fields were injured.

ADDISON, Philadelphia.

THE DEVELOPMENT OF BEHAVIOR IN FOETAL SHEEP. JOSEPH BARCROFT and DONALD H. BARRON, J. Comp. Neurol. **70**:477 (June) 1939.

Barcroft and Barron have observed over 100 embryos and fetuses of sheep, ranging from 22 to 143 days of gestation. As early as the thirty-fifth day after insemination spontaneous movements were observed. The forelimbs, although poorly developed, moved, as well as the neck and trunk. Between the thirty-ninth and the forty-fifth day the neck of the fetus grew at such a rate that the head-neck length was roughly equal to the length of the trunk. During this period the spontaneous activity appeared to be initiated and controlled by the head and neck. By the forty-seventh day the eyes were seen to move as part of the general activity. Between the fifty-second and the sixty-fifth day the limbs became more independent of the trunk. Activity was induced by faradic current in both the head and the trunk. The greater part of the spontaneous activity of the fetuses of sheep appeared to be due to impulses reaching the central nervous system by primary afferent neurons. As development proceeded spontaneous movements became progressively less extensive.

FRASER, Philadelphia.

MOTOR SEIZURES ACCOMPANYING SMALL CEREBELLAR LESIONS IN CATS. SAM L. CLARK, J. Comp. Neurol. **71**:41 (Aug.) 1939.

Twenty-three cats were used in these experiments. Methods of stimulation varied from merely wiping the exposed brain with a wisp of cotton to inserting a probe into the cerebellar substance for a short distance. The brains were later examined for extent of the injury. The results of slight mechanical stimulation of the cerebellum in the normal cat resembled the effects of electrical excitation of the same area, with certain differences. With mechanical stimulation the phases of both stimulus and rebound were sometimes absent and only the long after-effect appeared; or the phase of stimulus might be absent and both the phase of rebound and the long after-effect be apparent. With a more destructive mechanical stimulus, just as with very long electrical excitation, rolling movements and generalized effects occurred and seemed to prevent the appearance of the more delicately graded adjustments of the long after-effect. With properly controlled stimulation the seizure usually began with lifting of the homolateral extremity and then spread through the other parts of the animal. One cat had as many as eight spontaneous attacks in one day; at autopsy a localized abscess, about 2.5 mm. in diameter, was observed in the cerebellar cortex.

FRASER, Philadelphia.

THE ORIGIN, COURSE AND TERMINATIONS OF THE SECONDARY PATHWAYS OF THE TRIGEMINAL NERVE IN PRIMATES. A. EARL WALKER, J. Comp. Neurol. **71**:59 (Aug.) 1939.

Walker made lesions in the nucleus of the spinal tract of the fifth nerve in 3 adult specimens of Macacus mulatta and in the main sensory nucleus of the fifth nerve in 3 other macaque monkeys. Degeneration was allowed to proceed for fourteen days before the brain and spinal cord were prepared by the Marchi technic. In the first set of experiments the lesions not only extended through the nucleus of the tractus spinalis of the trigeminal nerve, but included the spinothalamic and spinocerebellar tracts as well as neighboring structures. Walker concludes that the degeneration of the majority of the crossed fibers is due to injury of the spinal nucleus of the fifth nerve. Such fibers cross the midline and lie between the inferior olivary nucleus and the pyramid. In the second set of experiments pontile and cerebellar structures were also involved. However, Walker analyzes the tracts and suggests that the secondary dorsal trigeminal tract is composed of both crossed and uncrossed fibers, the latter being more abundant.

ADDISON, Philadelphia.

VESTIBULAR NYSTAGMUS. A. DE KLEYN, Confinia neurol. **2**:257, 1939.

The reflex arc of vestibular nystagmus is composed of the peripheral labyrinth, the vestibular nerve, the vestibular nuclear area, the nuclear area of the oculomotor nerves, the oculomotor nerves and the ocular muscles themselves. Vestibular nystagmus can be elicited after removal of the cerebral hemispheres, after removal of the cerebellum, after section of the brain stem anterior to the nucleus of the abducens nerve and after section of the medulla caudal to the vestibular nuclei. The type and degree of nystagmus can be altered by stimuli which influence different portions of the reflex arc, such as the vestibular nuclei, the nuclei of the oculomotor nerves or the ocular muscles themselves, and by the combination and superimposition of varying types of nystagmus.

DE JONG, Ann Arbor, Mich.

THE REGULATORY INFLUENCE OF THE SYMPATHETIC ON BRAIN CENTERS. L. ASHER and N. SCHEINFINKEL, Confinia neurol. **2**:356, 1939.

Asher and Scheinfinkel carried out a series of investigations on the effect of sympathetic impulses on brain centers. They observed that stimulation of the cervical sympathetic trunk enhances the rise of blood pressure produced by clamping the carotid artery, either by increasing the extent of or by prolonging the rise or by both. Abolition of sympathetic impulses to the brain by local anesthesia causes the rise in blood pressure produced by clamping the carotid artery to be less in degree or less well sustained. After recovery from local anesthesia the vasomotor responses return to normal. The authors conclude that the sympathetic nervous system exerts an augmentary influence on the vasomotor centers of the brain, and probably also on other vegetative centers.

DE JONG, Ann Arbor, Mich.

A NEW TRIGEMINAL REFLEX (TRIGEMINOTYMPANIC REFLEX) BASED ON SELF OBSERVATION. F. ZAK, Confinia neurol. **2**:368, 1939.

Zak describes a reflex elicited by tactile stimulation of the skin of the cheek, with resulting contraction of the muscles of the cavum tympani and production of an endotic sound. The afferent arc lies in the trigeminal nerve and possibly also in the cervical nerves. Pain and temperature stimuli, especially cold stimuli, are also effective in producing the reflex. In extreme cases pain stimuli from the

entire body surface may precipitate the reflex phenomenon. Zak believes that there is a conditioned tactile trigeminotympanic reflex in addition to the known conditioned acoustic reflex.

DE JONG, Ann Arbor, Mich.

Psychiatry and Psychopathology

THE INITIAL NERVOUS SYNDROME OF PELLAGRA AND ASSOCIATED DEFICIENCY DISEASES. J. P. FROSTIG and T. D. SPIES, Am. J. M. Sc. **199**:268 (Feb.) 1940.

Frostig and Spies selected 60 cases of pellagra, in many of which the disease was associated with beriberi and riboflavin deficiency, and analyzed the symptoms and experiences reported by the patients. The symptoms were grouped under: (1) the elementary syndrome, consisting of psychosensory disturbances in all the special senses and the skin, of psychomotor disturbances, with an increase in motor drive and of emotional changes, in which increased excitability and sensitivity with a sad and gloomy mood prevailed, and (2) general symptoms of the central nervous system, with weakness and increased fatigability, sleeplessness and headaches. The authors emphasize that no connection was established between the experiences of the single personality and the initial nervous syndrome of pellagra. After the administration of large amounts of nicotinic acid, cocarboxylase or vitamin B_1 the symptoms diminished rapidly in intensity or disappeared entirely.

MICHAELS, Boston.

FOCI OF INFECTION IN PSYCHIATRIC PATIENTS. CHARLES HOWARD BROWN, Am. J. M. Sc. **199**:539 (April) 1940.

Brown reports that the incidence of foci of infection among 239 patients in the Henry Ford Hospital with mental rather than physical illness was 62.8 per cent. There was little difference in the incidence of foci of infection on the basis of the mental disease or the age of the patients in each disease group. Since the patients with foci of infection did not have arthritis or rheumatic heart disease, there must be some other physical condition present in patients who do have arthritis arising from foci of infection. The most common sites of the foci were the nose and throat (44 per cent), teeth (37 per cent), genital organs (22 per cent), urinary tract (17 per cent) and cardiorespiratory tract (1.6 per cent). The most common kinds of infection were chronic tonsillitis, chronic sinusitis, apical abscesses, pyorrhea, chronic prostatitis and chronic cervicitis. Other conditions were relatively common, arteriosclerosis being present in 12.8 and hypertension in 6.4 per cent. Of 50 cases of dementia paralytica, signs of syphilitic involvement of the heart or the aorta appeared in 17 per cent.

MICHAELS, Boston.

A FIVE TO TEN YEAR FOLLOW-UP STUDY OF 641 CASES OF SCHIZOPHRENIA. CHARLES RUPP and E. FLETCHER, Am. J. Psychiat. **96**:877, 1940.

Rupp and Fletcher examined, after a period of at least four and a half years, 641 patients who had been admitted for the first time with a condition diagnosed as schizophrenia. They found that 27.5 per cent were in the community and 53.5 per cent still in hospitals for mental disease; 5.1 per cent could not be followed. Of the 608 who could be observed, 6.6 per cent were much improved and 15.2 per cent improved. On studying the spontaneous rate of remission for the diagnostic subtypes, the authors found that the best results were obtained in cases not classifiable in a subgroup, and the next best results in the catatonic cases. They found that the age of onset was of little importance. Rupp and Fletcher observed further that the shorter the duration of the illness prior to hospitalization the better the prognosis, and that patients requiring hospitalization for more

than two years were less likely to show improvement than those hospitalized for a shorter period. Approximately 50 per cent of the patients left the hospital for at least one month, and the rate of readmission was in inverse ratio to the degree of improvement.

FORSTER, Boston.

IDENTIFICATION WITH THE ENEMY AND LOSS OF THE SENSE OF SELF. CLARA THOMPSON, Psychoanalyt. Quart. **9**:37, 1940.

Thompson points out that identification with a loved person is an important feature of the child's development. "Some individuals, because of early threats from destructive personalities in authority, identify with these personalities through fear. In the course of taking this step, critical attitudes towards the person in authority are suspended. In time the capacity for a conscious critical attitude is lost. The whole situation becomes a vicious circle. Identification with the enemy makes an already weak self more helpless and therefore more in need of handling later threatening object relationships by further uncritical identification. Finally, the patient can no longer have the feeling of living his own life. When the destructive identification is sufficiently great, possibly all sense of personal wishes or drives are lost. . . . In the cases where the damage is less extensive there remains some ability to distinguish between favorable and unfavorable situations. However, due to the fear of the enemy personality plus dependence on him, the critical faculty can only with difficulty come to consciousness, and this happens usually only after identification has taken place. In these cases the criticism usually appears as some attempt to disclaim responsibility for the act or attitude which has already been incorporated. It may be disclaimed by being made ridiculous like a caricature; or the individual denies that it is his own body experiencing the sensation; or he makes a general denial of reality. On what occasions one type of reaction appears rather than another is not clear. All methods have one quality in common: namely, the unacceptable aspect of the object has to be taken into the self before any even indirect recognition of its danger can be admitted. At the same time there occurs inhibition of any adequate expression of hostility."

Thompson cites 6 cases—3 of schizophrenia and 3 of schizoid personalities—to illustrate her thesis. In these cases, the patient at once made a marked identification with the analyst. The author points out "that because of the nature of the dependence of these individuals it takes very little to make the analyst, or any person on whom the patient leans, become a threat to him. A relatively innocent question asked at the wrong moment can do extensive damage because it cannot be rejected. Therefore, in treating these patients one must be constantly on the alert lest one unwittingly lead the patient into a situation contrary to his interests. All intervention on the part of the analyst must be made cautiously and with the awareness that any resulting disturbance in the reality sense means that the patient feels seriously threatened by the analyst. Such a situation must be straightened out at once."

PEARSON, Philadelphia.

Diseases of the Brain

SYNDROME OF PSEUDOBULBAR PALSY. ORTHELLO R. LANGWORTHY and FREDERICK H. HESSER, Arch. Int. Med. **65**:106 (Jan.) 1940.

Langworthy and Hesser use the term supranuclear bulbar paralysis instead of pseudobulbar palsy because it gives a better indication of the localization of the lesions. The corticobulbar fibers may be involved in the motor cortex, the internal capsule, the cerebral peduncle or the pons. The cardinal features for diagnosis are difficulties in speech, mastication and deglutition, without signs of injury of the bulbar nuclei. Forced laughing or crying and intellectual enfeeblement are common. The face in repose shows poverty of expression, and saliva may drip from the mouth. The symptoms may appear suddenly or gradually, and if the corticospinal tracts are involved quadraplegia results.

Swallowing is coordinated largely at a reflex level in cases of pseudobulbar palsy. Because of weakness of the pharyngeal muscles the patients have difficulty in expelling the mucus which collects. Coordination of breathing and swallowing is so poor that food may enter the bronchi. Since swallowing is difficult, saliva collects and drips from the mouth. During the initial period of shock, speaking is impossible. Phonation is almost always poor, because of weakness of the muscles of articulation. If the cerebellar pathways are involved as well as the corticobulbar tracts a cerebellar type of dysarthria results. Increased tone may appear in the palatal or the diaphragmatic musculature and influence phonation. The patient speaks in a nasal, monotonous, choppy, rapid manner. The words are often unintelligible, for the patient has difficulty in pronouncing labial and labiodental sounds. Respiration is jerky, and it is suggested that the medullary center is released from cortical control and overacts to blood-borne chemical stimuli. The paths of voluntary impulses to facial and respiratory muscles are undoubtedly the corticobulbar and corticospinal tracts. Injury of these tracts impairs volitional control of the muscles concerned so that they overact. There is little evidence for an exact localization of involuntary facio-respiratory control. An unusually active jaw jerk is an important sign of bilateral injury to the corticobulbar fibers. Mental deterioration of varying degrees and types is seen. Cataleptic periods and tonic perseveration, such as forced grasping and groping, may be present. The sucking reflex is often demonstrable.

Symmetric areas of softening of the motor cortex in the lower prefrontal area and in the operculum destroy the cortical control of the bulbar muscles. Most frequently the lesions are in the internal capsule, but pontile lesions may also be responsible. In the majority of cases pseudobulbar palsy results from cerebral vascular lesions. Arteriosclerosis or syphilitic vascular disease, with thrombotic softenings, may be seen. Embolic processes, disseminated sclerosis and Friedreich's ataxia may also give rise to the syndrome of pseudobulbar palsy.

BECK, Buffalo.

PICK'S DISEEASE. S. MILES BOUTON JR., J. Nerv. & Ment. Dis. **91**:9 (Jan.) 1940.

Bouton reports 4 cases of Pick's disease, with clinical and pathologic studies. In 2 men and 2 women the clinical course began at the ages of 50, 56, 52 and 55 years, and ended in death nine, seven, two and one-half and two years later, respectively. Commitment of the patients to a state hospital occurred at times varying from five years to six months after the onset of the disease. Clinically, all patients suffered from progressive dementia of varying rapidity, characterized by initial restlessness, mild loss of memory, more apparent than real, carelessness or incompetence, disturbances of the sleep rhythm and some emotional flattening or instability. Later, complete apathy followed, with marked speech difficulties in all 4 cases and definite aphasia in 3. Memory and orientation remained relatively intact in the midst of pronounced mental dilapidation. The common phenomena of senility were in evidence, with poor attention, interest in trifles, defect of judgment and purposeless activity, progressing steadily to more severe disturbances, such as mutism, loss of sphincter control, stupor and marked physical deterioration and trophic cutaneous changes, and eventually to death from cachexia or intercurrent infection. Neurologic changes were few and varied, giving no indication of focal lesions. Only 1 patient had a convulsion; delusions were few and poorly organized, and vascular changes were practically absent.

Pathologically, all 4 brains exhibited cortical atrophy proportionate to the chronicity of the process and usually bilaterally symmetric in distribution. The frontal lobes were most severely affected in all the cases, with involvement of the temporal lobes in 3 instances and of the occipital lobes in 1. The precentral and postcentral gyri were usually spared, and the parietal lobe was in general unaffected. There were marked atrophy of the convolutions and widening of the

sulci in the involved regions. The white matter was tough on cutting. These gross alterations were most obvious in the cases of long-standing disease. Microscopically, marked swelling, chromatolysis, nuclear displacement and some neuronophagia and loss of contour were observed in the ganglion cells of the cortex, with complete destruction of many cells in the severely affected regions. There were no senile plaques and few fibrillary changes of the Alzheimer type. Argentophilic inclusion bodies were not an outstanding feature. The difference in degree of destruction of the neurons in the variously affected areas was expressed almost exclusively in terms of the number of cells involved, and was not proportional to the difference in degree of gross involvement of the parts. The white matter was much less affected than the cortex and showed only mild degrees of rarefaction. Cortical gliosis was advanced in the more chronically affected brains, but was minimal in those in which the process was of shorter duration, this finding being in accord with the gross changes. The basal ganglia and cerebellum were practically unaffected. In no case was there any significant arteriosclerosis or grouping of the pathologic changes with regard to vascular supply. Bouton emphasizes the unreliability of encephalograms in the clinical diagnosis and recommends instead psychopathologic methods of examination, in particular those of Goldstein and Katz.

MACKAY, Chicago.

ANGIOBLASTIC MENINGIOMA WITH SYMPTOMS OF PARKINSONISM. K. H. KRABBE and C. J. MUNCH-PETERSEN, Confinia neurol. **2**:312, 1939.

Krabbe and Munch-Petersen report the case of a man aged 55 who experienced muscular rigidity of the right side, tremor of the hands, slowing of thought and motor reactions, loss of memory and generalized convulsions following a febrile illness. There was evidence of generalized arteriosclerosis. A diagnosis of Parkinson's syndrome with cerebral arteriosclerosis was made. However, the condition progressed. The convulsive seizures became more frequent and were followed by periods of transient aphasia. Ophthalmoscopic and roentgenologic examinations showed no abnormalities. The patient died; postmortem examination revealed an angioblastic meningioma in the left frontoparietal region.

DE JONG, Ann Arbor, Mich.

TUMORS OF THE BRAIN WHICH SIMULATE DEMENTIA PARALYTICA OR TABES. J. RUESCH, Schweiz. Arch. f. Neurol. u. Psychiat. **43**:149, 1939.

Ruesch reports 4 cases of meningioma involving the frontal lobe in which the antemortem diagnosis was either dementia paralytica or cerebrospinal syphilis. The Wassermann reaction of the cerebrospinal fluid was positive in 3 of them, including 2 in which the Wassermann reaction of the blood was likewise positive. Optic atrophy was observed in 2 cases; the pupils failed to react to light in the other 2, and in all 4 cases there were mental changes more or less characteristic of dementia paralytica. Two patients had dysarthria. In 8 cases of pituitary tumor, sluggishness or absence of the pupillary reaction to light was associated with sluggishness or absence of either the patellar or the achilles reflex. Optic atrophy was present in 7 of these cases, including 1 in which mental symptoms were noted. Optic atrophy, right hemiparesis and mental changes suggestive of dementia paralytica were noted in another case of pituitary tumor. In none of the cases of pituitary tumor, however, were positive serologic reactions for syphilis obtained. The Wassermann reaction of the cerebrospinal fluid was positive at the time of the first examination but negative six years later in a case in which there were a history of syphilis and progressive mental changes. Optic atrophy was discovered when the patient was first seen, and bitemporal hemianopia was demonstrated a year later. Autopsy revealed a meningioma involving the optic chiasm and the right frontal lobe.

Ruesch reports 4 cases of intracranial tumor in which syphilis was the first diagnosis and some form of antisyphilitic treatment had been given. The Wassermann reaction of both the blood and the cerebrospinal fluid was uniformly negative, but colloidal tests of the spinal fluid gave reactions consistent with neurosyphilis. The globulin content of the spinal fluid was increased in 3 cases. The first 3 patients had had syphilis, and the husband of the fourth was known to have the disease. The first patient, a man aged 45, complained of unsteadiness on his feet, forgetfulness, paresthesias of taste and unwonted slowness in performing his daily tasks. He was unable to solve simple problems in mental arithmetic, and his memory was slightly defective. The right pupil, which was dilated, did not react to light, and the left pupil reacted sluggishly; both were slightly irregular in outline and reacted poorly on convergence. The left patellar and right achilles reflexes were hypoactive; the left achilles reflex was absent. Bilateral papilledema was discovered a year later and, during a course of treatment with neoarsphenamine and bismuth, hemiparesis developed. A parasagittal meningioma was subsequently removed.

A man aged 49 had recently become emotional and childish. He had attacks characterized by sweating, redness of the face, occipital pain, tremor of the legs and inability to speak. The pupils, which were slightly irregular, reacted on convergence but did not respond to light, and slight paresis of the left facial nerve was observed. Six years later most of the extraocular muscles were either weak or paralyzed, and there was right facial paresis. The Babinski reflex was present bilaterally. Postmortem study revealed a glioblastoma multiforme of the thalamus and midbrain.

A man aged 42 complained of impaired vision in the right eye. Both pupils reacted sluggishly, and optic atrophy was present on the right side. Vision was subsequently lost in the right eye, and temporal hemianopia developed in the left. Roentgenologic study revealed erosion of the sella turcica, and the patient died after attempted removal of a huge adenoma of the hypophysis. A woman aged 58 complained of headache and failure of vision in her left eye. The pupils were small but reacted well. Optic atrophy was noted on the left side, and the right disk was pale. The patellar reflexes were sluggish, and the left achilles reflex was absent. Roentgenologic examination of the skull revealed nothing of significance, but later, when the presence of bitemporal hemianopia was demonstrated, erosion of the sella turcica was disclosed. Roentgen therapy was instituted.

Optic atrophy without papilledema is common in cases of pituitary neoplasms and of tumors lying beneath the frontal lobe. When observed before characteristic defects of the visual fields can be demonstrated it may be wrongly attributed to tabes. In the early course of "retrobulbar neuritis," before pallor of the disks has developed, sluggishness of the pupillary reaction to light may likewise be misinterpreted. Loss of smell, an important diagnostic sign of meningiomas of the olfactory groove, seems to be frequently overlooked. Weakness or absence of the tendon reflexes may be associated not only with neoplasms giving rise to generalized increase of intracranial pressure but also with tumors of the hypophysis. Mental symptoms encountered in cases of cerebral tumor are not altogether attributable to diffuse cerebral changes. Involvement of either the frontal lobes or the hypothalamus may give rise to symptoms which are suggestive of dementia paralytica.

A history of syphilis may be misleading. The existence of neurosyphilis does not exclude the possibility of intracranial tumor, and a positive Wassermann reaction of the spinal fluid is not always associated with anatomic evidence of syphilis of the nervous system. Such a reaction, especially when associated with pleocytosis, must nevertheless be regarded as a reliable sign of the disease. The various colloidal reactions, on the other hand, are less specific. Ophthalmologic examination is necessary in every case of psychosis of organic type. Should such an examination reveal constriction of the visual fields, central scotoma, temporal pallor of the disks or even pronounced optic atrophy, roentgenologic study of the skull is indicated.

DANIELS, Denver.

Vegetative and Endocrine Systems

ON THE ROLE OF THE PITUITARY STALK IN THE REGULATION OF THE ANTERIOR PITUITARY, WITH SPECIAL REFERENCE TO THE THYROTROPIC HORMONE. U. U. UOTILA, Endocrinology **25**:605 (Oct.) 1939.

Uotila reports the effects on rats of section of the pituitary stalk combined with exposure to cold. The specific points of interest are: (*a*) the effect of section of the stalk on the thyroid, adrenals and gonads and on growth; (*b*) the effect on these glands of section of the stalk followed by cold, and (*c*) the effect on these glands of cold after blank operations. After section of the pituitary stalk in rats enough thyrotropic hormone is produced under ordinary conditions to keep the thyroid histologically normal. However, section of the stalk followed by exposure to cold prevents the increased secretion of the thyrotropic hormone and hypertrophy of the thyroid, which normally occur in intact animals on exposure to cold. This negative effect is not due to general pituitary insufficiency. Hence, it follows that in animals exposed to prolonged cold the hypothalamus stimulates the secretion of the thyrotropic hormone by impulses transmitted through the pituitary stalk. The role of the pituitary stalk in this regulation is more important than that of the cervical sympathetic fibers. The adrenals in rats remain normal and react normally to cold with hypertrophy after section of the pituitary stalk as after cervical sympathectomy. Corticotropic secretion is hence probably under humoral control.

After section of the pituitary stalk in rats, the testes and seminal vesicles remain normal, but the usual damaging effect of cold on spermatogenesis is abolished. Hence, the influence of temperature on the secretion of gonadotropic hormones must be to a certain extent under hypothalamic control. Section of the stalk does not significantly affect the growth of rats. The anterior lobe of the pituitary is believed to have a basic secretory rhythm, largely under humoral influence, which is independent of the pituitary stalk under ordinary conditions. Nevertheless, available evidence indicates that the hypothalamus and the pituitary stalk participate in the regulation of secretion of the anterior lobe of the pituitary gland in specific adjustments to certain environmental situations. In Uotila's experiments evidence is adduced to indicate such mediation of the stalk on prolonged exposure of the animal to cold.

PALMER, Philadelphia.

THE PART PLAYED BY AGE AND THE FEMALE SEX HORMONES IN RESISTANCE TO INFECTION. D. H. SPRUNT, Endocrinology **25**:625 (Oct.) 1939.

In four experiments in which castrated rabbits used as controls were compared with castrated rabbits receiving estrogen it was found that 33.4 per cent of vaccine virus was neutralized by estrogen. In three experiments in which normal adult male rabbits were compared with adult pseudopregnant rabbits it was found that 46.2 per cent of the virus was inactivated. It was seen from these experiments that age and the sexual endocrine pattern have an effect on the dispersion and concentration of disease agents in the skin. Concentration of vaccine virus is shown to be favorable to the host. It should be borne in mind, however, that concentration of the disease agent is not necessarily to the advantage of the host, as it has been shown that dispersion of moderately virulent bacteria leads to their being overcome by the host. Sprunt shows that age increases the ability of the body to produce antibodies, that certain of the "sex hormones" can change the tissues so that resistance to infection is changed, that the dispersion or concentration of disease agents is affected by the endocrine pattern of the host and that this concentration or dispersion affects the host's resistance to disease,

PALMER, Philadelphia.

Cerebrospinal Fluid

A Study of the Clinical Aspects and Mechanism of Development of Hypertension of the Cerebrospinal Fluid in Hypertensive Disease. Morris M. Kessler, Eli Moschcowitz and Nathan Savitsky, J. Nerv. & Ment. Dis. **90**:594 (Nov.) 1939.

Kessler, Moschcowitz and Savitsky studied 22 patients with advanced arterial hypertension with special reference to the incidence of elevated pressure of the cerebrospinal fluid, papilledema and other retinal changes and the permeability of the hematoencephalic barrier. Observations were also made on the venous pressure as measured directly in a cubital vein, and on the urea content of the blood, the renal function and the incidence of headache. The pressure of the cerebrospinal fluid was regarded as elevated when above 200 mm. of water, while venous pressure was considered as increased when greater than 9 cm. of water. In measuring the permeability quotient of the hematoencephalic barrier, sodium bromide was administered in proportion to the patient's body weight, after which the bromide content of the blood was compared with that of the cerebrospinal fluid. The ratio between the bromide content of the blood and that of the cerebrospinal fluid varies normally from 2.8 to 3.5. In this study, ratios below 2.0 were considered as evidence of increased permeability. Headache was present in practically all cases in which the diastolic pressure was more than 120 mm. of mercury, but was rare with lower diastolic pressures. Papilledema was present in 14 cases and appeared to result from three factors, acting separately or in combination: 1. Increased permeability of the hematoencephalic barrier was the most important, but not an essential, factor in the production of papilledema, since in every case in which the quotient was less than 2.0 papilledema was found; however, in 4 of 11 cases in which papilledema was exhibited the permeability was not increased. 2. Increased venous pressure was also important, but was not essential. Of 11 patients with increased venous pressure, 6 exhibited papilledema; of 14 patients with papilledema, 7 had no elevation of venous pressure. 3. Increased pressure of the cerebrospinal fluid was discovered in 9 of 21 patients. Six of these 9 subjects had a permeability quotient of less than 2.0. Of 14 patients with papilledema, 7 had increased pressure of the cerebrospinal fluid. There was no consistent relationship between papilledema and disturbance in renal function. Low intraocular tension facilitates the appearance of papilledema.

Kessler, Moschcowitz and Savitsky believe that the pressure of the cerebrospinal fluid is increased in cases of arterial hypertension by two factors: (*a*) sustained elevation of venous pressure, and (*b*) increased permeability of the hematoencephalic barrier. Venous pressure results from failure of the right ventricle and raises the cerebrospinal pressure by producing intracranial venous engorgement or by increasing the permeability of the barrier and so leading to the increased production of cerebrospinal fluid. Increased permeability of the barrier results chiefly, however, from capillary sclerosis consequent on the arterial hypertension. Systemic arterial pressure, no matter how high, does not increase the cerebrospinal pressure directly, but acts only indirectly through the mechanisms described. Osmotic changes resulting from disturbed metabolism have little or no effect on the cerebrospinal pressure.

Mackay, Chicago.

Coagulability of Cerebrospinal Fluid by Heat and Its Diagnostic Significance. M. Bock, G. Lemmen and H. Rosegger, Wien. Arch. f. inn. Med. **33**:113 (Oct. 10) 1939.

According to Bock and his associates, the phenomenon of heat coagulation of protein bodies has not been fully explained as yet, but among the numerous factors which play a part the following deserve special attention: 1. A certain number of

electrolytes in solution is necessary to effect heat coagulation; the lowest concentration which permits the development of concentration is designated as the "electrolyte threshold." 2. The protein bodies must be present in a certain concentration; if this "suspension threshold" is not reached visible flocculation does not take place. On the basis of these observations, Weltmann developed the method which he designates as the "coagulation band." In this method a constant dilution of serum (fiftyfold) is combined with arithmetically graduated concentrations of calcium chloride. The favorable diagnostic results that were obtained with Weltmann's heat coagulation test led to attempts with "heat coagulation of the cerebrospinal fluid." The heat coagulation of the cerebrospinal fluid determines (1) that number of test tubes of a series of concentrations of calcium chloride in which coagulation is perceptible and (2) the intensity of this flocculation and of the simultaneously observed turbidity. The authors describe the various intensities of flocculation and say that the flocculation curves are differentiated into normal, doubtful to weakly positive and positive types. They further determined whether under the conditions of the heat coagulation the determination of the electrolyte threshold was possible and of diagnostic value. They summarize the diagnostic value of the heat coagulation method on the basis of one hundred and twenty tests. The sugar and sodium chloride contents of the cerebrospinal fluid showed no parallelism with the outcome of the heat coagulation test. In all spinal fluids in which the coagulation test gave definitely pathologic curves the cell count and Pandy's reaction also indicated pathologic conditions, and Nonne's reaction did so in the majority of cases. Thus the heat coagulation test corroborates the fact that pathologic changes exist in the spinal fluid. The intensity of the flocculation and the number of test tubes in which it is observable are a measure of the severity of the changes in the cerebrospinal fluid. In cases in which only the cell count is slightly increased the pathologic outcome of the heat coagulation test may be of value, for in these cases the result is slightly more sensitive than the other protein reactions.

J. A. M. A.

Treatment, Neurosurgery

THE MALARIAL TREATMENT OF GENERAL PARESIS. ISRAEL KOPP and HARRY C. SOLOMON, Am. J. Syph., Gonor. & Ven. Dis. **23**:585 (Sept.) 1939.

Considerable difference of opinion has arisen in regard to the number of hours and the height of fever that should be produced in patients with dementia paralytica. The authors attempted to determine the amount of fever (malaria) experienced by a large group of patients with neurosyphilis and to correlate the height and total amount of fever with the clinical and serologic results. The oral temperatures were recorded hourly, and the number of hours of fever in which the temperatures were over 100 F. was computed. The best results were obtained in cases in which more than one hundred and fifty hours of fever with temperatures above 100 F. was employed. The number of hours of fever with temperatures at 104 and 105 F. made no significant difference in the clinical results. Patients who had more than ten paroxysms showed more improvement than those who had less than ten. Neither the frequency of the paroxysms nor the height of the fever was specifically significant.

The changes in the spinal fluid did not differ in the groups of patients with maximum temperatures of 104, 105 and 106 F. Regardless of the maximum temperature, the percentage of negative serologic reactions seemed to increase with each successive year following malarial therapy. Eighty per cent of the patients experienced definite arrest of the disorder after treatment with malaria and chemotherapy. The amount of improvement was found to depend largely on the amount and localization of damage to the brain and the underlying personality of the patient.

BECK, Buffalo.

THE TREATMENT OF HYPOGENITALISM IN THE MALE WITH THE GONADOTROPIC PRINCIPLE OF PREGNANT MARES' SERUM. R. H. KUNSTADTER, Endocrinology **25**:661 (Nov.) 1939.

Kunstadter treated 14 boys between the ages of 6½ and 14¾ years who presented hypogenitalism or cryptorchidism or both by the intramuscular administration of a preparation of pregnant mares' serum (gonadogen). Definite improvement, as evidenced by growth of the genitalia, appearance of secondary sex characteristics or descent, partial or complete, of undescended testes, occurred in 8, or 66.66 per cent of the patients. Cryptorchidism was present in 11 of the 14 patients—pseudocryptorchidism in 4 and true cryptorchidism in 7. In the latter group complete descent of one or both testes occurred in 3 and partial descent in 2 patients. Two patients with cryptorchidism did not respond to treatment. There was no change in the distribution of fat or loss of weight in any of the patients. It is believed that mare's serum is of definite value in treatment in certain cases of hypogenitalism and cryptorchidism. As yet the optimal effective dose has not been established, but the author believes that 50 to 100 units, three times a week, intramuscularly, probably will be more effective than the 10 to 20 units three times a week administered intramuscularly to his patients. With the higher dose results would probably be obtained in a shorter period. Of the 14 patients treated, local reactions occurred in 4 (28.5 per cent) in spite of the negative, or very mild, reaction to the preliminary intradermal test. Of the 4 patients, treatment of 2 had to be discontinued because of the severity of the local reactions. Systemic reactions did not occur in any of this group. However, a girl aged 12 experienced headache, vomiting spells and a temperature of 102 F. following a second injection (20 units) of this preparation.

PALMER, Philadelphia.

OBSERVATIONS ON THE ROLE OF VITAMIN B_1 IN THE ETIOLOGY AND TREATMENT OF KORSAKOFF PSYCHOSIS. KARL M. BOWMAN, ROBERT GOODHEART and NORMAN JOLLIFFE, J. Nerv. & Ment. Dis. **90**:569 (Nov.) 1939.

The criteria for the diagnosis of a Korsakoff psychosis in this study were amnesia for recent events, disorientation and confabulation. Of the 51 patients studied, 31 were designated as having a Korsakoff psychosis with acute onset, because of the additional presence of delirium, encephalopathy or acute hallucinosis. The remaining 20 patients presented only the classic triad, and their disease was classified as psychosis of insidious onset. On admission, all patients were given a diet of borderline adequacy in vitamin B_1 for an average period of eleven days. During this period 15 patients were discharged, 6 having recovered. The 36 remaining subjects then received a diet rich in vitamin B_1 with added vegex to furnish an estimated thiamine content of 3.3 mg. daily. Fifteen patients received no further treatment, while the remaining 21 were given an additional 10 to 50 mg. of thiamine chloride daily by injection. Of the 15 patients treated with the diet plus vegex, only 1 (6.6 per cent) recovered, while 10 (47.6 per cent) of the 21 receiving additional thiamine parenterally recovered. Of the 31 patients with psychosis of acute onset, 5 (16.1 per cent) recovered on the diet of borderline adequacy alone. Of the 8 patients with psychosis of acute onset given the diet plus vegex, only 1 (12.5 per cent) recovered, and of the 16 patients who received additional thiamine chloride parenterally, 9 (56.2 per cent) recovered. On the other hand, 20 patients whose psychosis had been of insidious onset fared poorly, since only 1 (5.0 per cent) of the patients on the diet of borderline adequacy, none of those on the diet plus vegex and 1 (20 per cent) of the 5 given additional thiamine parenterally recovered.

Bowman, Goodheart and Jolliffe admit the difficulty of drawing conclusions from these figures because of the possible factor of spontaneous recovery, but emphasize that subjects receiving injections of thiamine chloride showed an incidence of recovery approximately seven times as great as that shown by patients treated by diet alone.

MACKAY, Chicago.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY

H. Douglas Singer, M.D., *President, in the Chair*

Regular Meeting, Dec. 7, 1939

Insulin Therapy of Schizophrenia in the Elgin State Hospital, with Special Reference to Relapses and Failures. Dr. Gert Heilbrunn and Dr. Ruth Sternlieb, Elgin, Ill.

The results obtained at the Elgin State Hospital in the treatment of 315 schizophrenic patients during a period of three years continue to approximate those previously presented: The percentages of recoveries and of social remissions were 72 and 10, respectively, for the group of patients with a psychosis of less than seven months' duration, 35 and 20, respectively, for the group who had been ill from seven to eighteen months, and 10 each for the group who had been ill over eighteen months. Similar results were obtained with patients who had previously undergone a course of metrazol convulsion therapy with no improvement. Induction of an adequate number of shocks (fifty) was considered to be of importance, since several patients had not shown improvement before the forty-fifth shock. It is useless to produce a higher number of shocks unless sufficient response is shown prior to that point. The average number of shocks for successfully treated patients was thirty-five. No fatalities or lasting serious complications were encountered. The dose was kept as low as possible, and the patient was never allowed to go into shock unless he had failed to show improvement with induction of five or six hypoglycemic states. The first five shocks lasted from ten to fifteen minutes, the next five fifteen minutes longer, and so on, unless improvement had been noted. At no time, however, was the duration of shock longer than ninety minutes. No therapeutic benefit was derived from epileptiform seizures, which occurred in 33 per cent of all cases, but in only 24 per cent of cases in which treatment was successful. Roentgen examinations of the spine in a sample group of patients who had had between one and twelve epileptiform attacks did not reveal any fractures. Metrazol convulsions produced during the precomatose state of insulin hypoglycemia did not benefit patients who had been given both insulin and metrazol without success prior to treatment with the combined drugs. For this reason and also because of the disproportionately severe toxic changes in the cerebral ganglion cells of similarly treated rabbits, this modification was discontinued. Fifteen per cent of the patients in the first two groups who recovered or were greatly improved had relapses. No definite criteria for a future relapse could be established from the patient's history or the symptoms during the psychosis. A past spontaneous recovery, however, was presumptive warning of a future relapse. The slightest evidence of instability during the interval was almost invariably followed by a new outbreak of psychotic symptoms in a very short time. The symptoms in the first and the second attack were almost identical in all but 2 patients. The relapses occurred usually within six months after discontinuance of the treatment and became less numerous as time went on. A number of unsuccessfully treated patients with a psychosis not exceeding eighteen months' duration were compared with an equal number of patients from a group who had recovered with regard to the symptoms of the psychosis and the evaluation of the patients' personality factors. The study failed to furnish any fundamental differences. A practical prognostic help was found in the patient's reaction to the intravenous administration of sodium amytal. The schizophrenic patients who showed little

or no response to injections of sodium amytal failed to improve under insulin treatment, whereas a large percentage of those in whom it was possible to obtain a lucid period with sodium amytal responded favorably to insulin therapy.

DISCUSSION

DR. CHARLES F. READ, Elgin, Ill.: This paper represents the continuation and collaboration of a report made before the Chicago Neurological Society in April 1938 (Read, Charles F.; Heilbrunn, Gert, and Liebert, Erich: Insulin Shock Therapy: Report of One Hundred Cases, ARCH. NEUROL. & PSYCHIAT. **40**:1274 [Dec.] 1938). There are difficulties which arise in deciding on the duration of psychosis in any given case. In some cases the illness appears to be of sudden origin and later it may develop that the person had probably been sick for a considerable time before the symptoms became obvious. One always must consider this in determining the statistics of recovery and improvement on the basis of duration of the psychosis.

Dr. Heilbrunn, with many other authors, has used the term "spontaneous recovery" in contradistinction to recovery produced by shock therapy. The word "spontaneous" should be used in quotation marks because, unless the patient is at home, the effect of hospital treatment may have a great deal to do with the recovery. Many factors must be considered in evaluating the cause of the so-called spontaneous remission.

I think Dr. Heilbrunn has dealt satisfactorily with the statistical evaluation of relapses. These patients do recover and go home, and then they return at varying intervals; so at Elgin we have decided to call them recovered only if such recovery has endured for at least twelve months.

The full significance of Dr. Heilbrunn's statement concerning the treatment of patients previously treated with metrazol may not have been noted. It means that at this hospital the percentage of recoveries following insulin shock among patients treated formerly with metrazol, with failure or perhaps slight improvement, approximates that for the group of patients who have not been treated at all. Like many others, I long since have come to the conclusion that insulin shock is much more efficient than metrazol in treatment of schizophrenia.

Parenthetically, I may add, however, that my esteem for metrazol shock therapy is rapidly increasing. It accomplishes wonders for the depressions, especially those of later life. Since this paper was written a few patients with dementia praecox treated with insulin without success have shown marked improvement after metrazol shock.

This paper, as Dr. Heilbrunn has stated, presents a certain consistency of results obtained in one clinic by the same physicians in charge of treatment, as determined for patients with psychoses of the same duration during periods of one year, a year and a half and two years, respectively. In each of the check-ups the statistics have remained fairly consistent, so that the findings have some value.

I call attention to the low dose of insulin used. Dr. Heilbrunn begins with small doses, from 10 to 15 units; there have been no deaths or alarming coma reactions. An attempt has been made to determine why relapses occur and why of two patients with apparently similar histories and similar prepsychotic makeups, one recovers and the other does not. We are still in the dark as to why this occurs. Why some patients show excellent results, make a good recovery and then relapse we do not know. Studies are being carried on now to determine what, if any, personality trait may be considered malignant with respect to recovery under treatment.

DR. R. P. MACKAY, Chicago: It is astonishing to hear that treatment with insulin gave the same percentage of recoveries in cases in which metrazol had previously failed as in those in which no treatment had been administered. This would at first seem to indicate that metrazol is of little value. I doubt, however, whether this is a legitimate way of interpreting these statistics. To be fair, one

should consider a similar group of cases in which the treatment with metrazol followed failure with insulin. In a case in which metrazol has failed and insulin has subsequently given good results, one should consider the results as due not to the use of insulin alone, but to the use of metrazol and insulin. One must be cautious in interpreting these figures as evidence against the efficacy of metrazol.

DR. J. V. EDLIN, Chicago: I heartily agree with two points made by Dr. Read: First, the number of spontaneous remissions at the hospitals may be smaller than that in the homes, and second, estimation of the duration of the psychoses may be difficult.

I agree with Dr. Mackay that it is wise to remember that metrazol may be of value when insulin fails. At the Chicago State Hospital on occasion recovery has been obtained when insulin had been used first without success. It is my impression that at the Elgin State Hospital the authors have had the same experience, but probably did not state it in that way. There are certain types of patients for whom it is preferable to use metrazol first. In the case of a catatonic patient in an excitable state, it would not be feasible to use insulin first because of the difficulties of keeping the patient in bed.

As to relapses, I think the figures are reasonable and have been worked out carefully.

DR. JULIUS I. STEINFELD, Desplaines, Ill.: One must consider the schizophrenic spell as an acute manifestation of a schizophrenic personality, and if one wishes to effect a cure one must study the emotional makeup of the patient. In analysis it will be found that there are complicated emotional situations reaching far back into early childhood. A patient showed partial recovery after shock treatment and then became approachable for psychoanalysis. It was some time before she started to talk; then she confessed resentment against a beloved mother. I discussed with her her ambivalence conflict, her frustration and other conflicts. She improved remarkedly. It could be shown in this case that a patient partially improved by shock treatment can become adjusted if psychoanalytically approached. Another patient, ill for over three years, who was treated with insulin and metrazol for a long period did not show any signs of improvement. When he was finally subjected to "deep shock" he for the first time showed a lucid period, followed by gradual improvement. In this case, also, analytic approach after the shock treatment revealed important life conflicts, the discovery of which helped to bring about adjustment.

I take the point of view that in many instances one must treat acute symptoms with shock treatment, but the personality study must follow, especially when the patient is resistive to treatment or the disease has had a long duration.

DR. JACK WEINBERG, Chicago: I wish to confirm Dr. Heilbrunn's statement with regard to the success of insulin therapy in cases in which metrazol has failed. In some cases of failure with metrazol my colleagues and I have had excellent results with the use of insulin; some of the patients recovered completely, and some had only a social recovery. The onset of the illness of the patients who showed improvement was comparatively recent.

Dr. Mackay is right in suggesting that one should place under metrazol therapy patients who have failed to respond to insulin. Low and Goldstein and their associates have pointed out the success of multiple therapy in schizophrenia; many times when insulin has failed, metrazol has been effective.

DR. C. A. NEYMANN, Chicago: Some have concluded that in manic-depressive psychosis and schizophrenia one is dealing with life patterns which have been modified to suit the needs of the individual person. The rate of recovery of patients with mild or doubtful schizophrenia, whether treated with insulin or with metrazol or not treated at all, is much greater than that of patients with outspoken, clearcut disease. Persons with mild forms are also much less likely to have recurrent attacks of the disease. One must bear in mind that there are patients with schizophrenia who recover and then, after a certain interval, have

a second, third or even fourth and fifth attack, with complete recovery following each recurrence of the psychosis. There are also patients with manic-depressive psychoses who, after many attacks, reach an end stage of the disease with a certain amount of deterioration. I wish to ask Dr. Heilbrunn whether many extrovert features were observed among the schizophrenic patients who recovered, and what were the introvert features of the manic-depressive patients who recovered. In other words, how many patients who recovered had borderline, mixed psychoses. Persons with borderline conditions showing features of both manic-depressive psychosis and schizophrenia have a high rate of recovery, with or without treatment. There seems to be a balancing of life patterns in this group of patients with the mixed type.

I assume that little or no psychotherapy was used in conjunction with shock treatment. It might be valuable to follow a group of patients treated with a maximum amount of psychotherapy after the so-called recovery, remission or social adjustment, and compare the final outcome with that in a group of patients sent back to their former environment without any attempt at psychic adjustment.

This leads me to two questions: How many manic-depressive attributes are present in schizophrenic subjects, and how many schizophrenic attributes in manic-depressive subjects? What is the relative importance of the psychic influence produced by the shock and of the helpful attitude of the physician during or after the period of recovery?

DR. GERT HEILBRUNN, Elgin, Ill.: In reply to Dr. Mackay, I did not claim that insulin is better than metrazol; I have seen a parallel group of patients who failed to respond to insulin and were then treated with metrazol without marked success. A few patients treated with metrazol after insulin showed favorable results; this, I think, answers Dr. Edlin's question also.

As to the diagnostic preference for selection of patients: When paranoid patients are treated with insulin and patients with mute stupor with metrazol, we, at Elgin, have observed no difference between the two groups in response to treatment.

I agree with Dr. Steinfeld that personality studies must be employed; Dr. Read mentioned that the analytic approach in Elgin is in use and will be continued.

In answer to Dr. Neymann, a peculiar feature was noted in the study of these patients. The patients who did not respond to insulin showed more manic features than those who did. If one can speak of borderline psychoses, there were certainly more cases of this type among the groups of patients who did not recover than in the groups who did. With reference to Dr. Neymann's second question, we did not carry out any organized psychotherapy. When shock therapy was inaugurated this question was often raised: Do the patients receive more attention, and is that the real reason why they respond? It is known that, especially in private institutions, the patients receive much attention and do not improve because of this. Our patients treated with shock did not receive more attention than they would have if they had not been treated with insulin.

Integration of the Autonomic Nervous System in Schizophrenia: A Day by Day Study of a Schizophrenic Patient. DR. JOSEPH C. RHEINGOLD, Chicago.

The aims in the study of this patient were (1) to make daily observations of the behavior and the physiologic functions of the patient and of the meteorologic changes, and to correlate the three sets of variables, and (2) to gain an impression of the variability of the physiologic functions.

A man aged 25 had a history of lifelong inadequacy. The acute illness, characterized by auditory hallucinations, to which he reacted with fear, queer acts and insomnia, began about a month prior to his admission to the hospital. The condition was classified with the schizophrenias. The patient was observed from June 4, 1937 to July 8, 1938, during which time daily determinations were made

of the body temperature, pulse rate, respiratory rate, blood pressure, weight, hydrogen ion concentration and carbon dioxide content of the venous blood, absolute leukocyte count, differential leukocyte count, strength of the hand grip and electrical resistance of the punctured skin of the forearm; weekly determinations were made of the rate of oxygen consumption. The results were analyzed statistically and were charted on a multiple ordinate graph with a time abscissa, together with a meteorogram of the period and a scale of clinical change.

During the first three months, the control period, the patient received no treatment. Then, in succession, he was treated with metrazol, pitressin, insulin, sodium citrate, induction of fever and a second course of metrazol. Only the physiologic and clinical findings in the control and the first period of metrazol treatment are included in this report.

During the control period the organism was in a hypometabolic state: there were hypothermia, bradycardia, a relatively small "respiratory area," hypotension, reactive alkalemia, relative lymphocytosis, relatively high electrical resistance and low basal metabolic rates. All of these factors were highly variable. As the patient was almost uniformly stuporous throughout this period, no correlations could be drawn between physiologic and clinical changes.

After the third injection of metrazol (and coincident with the meteorologic instability of early fall) clinical improvement was rapid. After about two weeks of adjustment in behavior there was rapid decline of energy to the stuporous level before treatment, with interruption in the form of several days of excited, intractable behavior. Throughout the period the metabolic status, except for relative acidemia, was normal.

The changes observed during this period may be interpreted in one of two ways: (1) metrazol (or metrazol and the weather) induced sympathetic stimulation and heightened levels of metabolism, which mobilized energy for adjustment to the environment, or (2) the experience of the treatment (which the patient regarded as punishment) removed a psychologic block and released energy, which was used first in adapted behavior and later in frank aggression against the environment.

DISCUSSION

DR. A. A. LOW, Chicago: One may ask: 1. What is the practical value of this study? 2. What is its theoretic value? 3. Is the method which was applied correct and systematic? The practical value of Dr. Rheingold's investigation is limited, because it is a study of 1 case. As he mentioned, only a few such cases have been studied and reported in the literature; their practical significance is that they may spur others to engage in similar work. In addition, this case is, to my knowledge, the first in which day to day studies of this kind were made on a patient treated with metrazol.

One may ask: Could the study of this case be made more valuable by selecting one variable as an index to the total metabolic activity? None of the variables which were investigated seems to be capable of serving as such an index. Indeed, Dr. Rheingold emphasized that the total behavior of the patient can be judged only from his clinical conduct. That, of course, is unsatisfactory.

Whether this study can contribute to the theoretic knowledge of schizophrenia I do not know.

I wish to ask whether, if one did not know anything about the clinical behavior of the patient, these charts would tell anything. Perhaps more studies of this type are needed before this question can be answered.

Was the selection of the variables a wise one? Could the author have chosen better variables? I wonder if the nitrogenous substances could not have been considered.

DR. ISIDORE FINKELMAN, Chicago: I wish to ask Dr. Rheingold why he used pitressin. What changes were produced by this drug? It is interesting that when

the normal person is given injections of pitressin it produces a strong urge to evacuate the colon; this does not occur in patients with dementia praecox.

DR. DAVID SLIGHT, Chicago: Did I understand Dr. Rheingold to say that these observations were taken daily under basal conditions? Did Dr. Rheingold have the opportunity to note whether there was any diurnal variation, such as occurs in normal persons, with regard to the temperature and the electrical resistance of the skin? As to the measurement of electrical resistance, possible variations may not have been recorded, as the skin was punctured. There are large variations and fluctuations in the skin, but much lesser, or even doubtful, variations in electrical resistance in the general body tissues, exclusive of the skin.

Did Dr. Rheingold have the opportunity to make observations on the mental condition of the patient during the period of increased activity noted on his records? Was there any correlation between the degree of social activity or the interest of the patient in his surroundings and the instrumental observations? This would seem a fundamental issue.

DR. FRANZ ALEXANDER, Chicago: In line with Dr. Slight's remarks, I should say that the physiologic changes observed here correspond roughly to changes which one would observe in any normal person under strong emotional tension. I was interested in Dr. Rheingold's brief reference to the fact that this patient became more aggressive. It is well known that during such aggressive emotional states the blood pressure and the basal metabolic rate rise and changes in respiration are also observed. It would seem, therefore, that one is dealing in this case with a change of emotional tonus. Under metrazol treatment the patient assumed a more aggressive, outgoing emotional state, which necessarily would produce a physiologic change of this type. It would be interesting to drive such a patient into increased physical activity to see whether it would vitalize his metabolism and produce the same physiologic changes as a result of his increased activity. Could not one interpret all the physiologic changes observed as due to increased tonus of the sympathetic nervous system resulting from an increased aggressive mood and the correspondingly higher rate of physical activity?

DR. J. C. RHEINGOLD, Chicago: The selection of tests, I am afraid, was determined for me by the laboratory assistance available. If I had had a free hand in the matter I should like to have followed the nitrogen, sugar and lipoid metabolism, but I was limited to one or two blood chemical determinations and selected the p_H and the carbon dioxide content of the blood. I was interested primarily in the physiologic status of the total organism rather than in single functions. My intention now is to cut down this battery of tests. I thought it well at the beginning to use as large a battery as possible, and to apply it for as long a time as possible, in order to get an idea of which variable best represents the status of the organism.

In response to Dr. Finkelman's question, the patient did not show acute distress after administration of pitressin. The blood pressure fell readily during the period of administration. One could have anticipated that, for work done in the department of pathology at the University of Illinois has shown that with repeated injections of pitressin the blood pressure falls. However, prior to the period of daily treatment with 20 units of pitressin I gave the patient a single injection, and there was a fall in blood pressure.

The basal conditions under which the tests were made were those observed during a basal metabolic test. I made no study of diurnal variation. I punctured the skin in order to eliminate the resistance offered by the horny layer, and to measure the resistance of the living tissues. That one has here an index of metabolic activity is suggested by the relatively high level of resistance during the control period and the relatively low level during the period of metrazol treatment, with its greater metabolic activity.

The attempt was made to correlate the behavior with physiologic variations, but the stuporous behavior afforded little opportunity. I was not able to gain

much insight into the content of the patient's mind, but it appeared that there was a good deal of hostility that was kept down.

The metabolic swing may have come in the wake of released aggression. On the other hand, metrazol may have induced sympathetic stimulation, possibly stimulation of the thyroid and adrenal glands, and the mental state have improved as a consequence.

Methyl Guanidine Sulfate and Its Possible Use As a Therapeutic Agent for Mental Disorders. Dr. John J. Madden and Dr. Leo A. Kaplan, Chicago.

Our work began after the observation of improvement in behavior in a case of schizophrenia following an accidental first and second degree burn while the patient was being given a bath. Prior to the burn the patient had presented symptoms of withdrawal that frequently amounted to catatonia. At the time of the accident the patient made no outcry and seemingly was oblivious to the injury. A considerable area of the integument was involved, and about one half of the region was burned to second degree proportions. Elevation of temperature to 103 F. followed shortly and continued for three or four days. During this time steady improvement took place in the patient's mental state and after about one week he was in a sufficiently improved condition to be released from the hospital. Details of this case have been reported elsewhere (Madden, J. J., and Rickels, N.: *Illinois M. J.* **75**:373 [April] 1939).

Impressed by the improvement in the mental state of this patient, we considered the possibility that the burn may have been a therapeutic agent in recovery, although we also realized that the change in the patient following the burn may have been brought about by other factors. Among these, the profound psychologic effects of the accident and possibly other accidental dynamisms, not fully understood, were considered. Since considerable interest is now devoted to efforts to uncover an organic background for schizophrenia, we sought some chemical agent that may have produced metabolic changes which were reflected in the alteration in personality.

We decided to treat patients with schizophrenia with blood serum or whole blood withdrawn from persons who had been severely burned. A series of suitable patients with schizophrenia was selected, and serum or whole blood was injected both intramuscularly and intravenously. We began with small doses and increased the amounts until the upper limits of physiologic tolerance were reached. In this small series, of 6 patients, the final optimum intravenous dose varied from 10 to 20 cc., three or four times a week. The initial reaction consisted of generalized peripheral vascular dilatation, accompanied by an erythematous flush and a moderate amount of diaphoresis; the pulse rate was lowered regularly from 10 to 15 beats per minute. Respiration was unaffected. A small upward fluctuation in the systolic and diastolic blood pressure took place. The subsequent course of events is illustrated by the following short clinical report of the progress of one of the patients in the series during this treatment.

C. U., aged 28, was negativistic, lacked insight and exhibited many bizarre facial mannerisms and grimaces. After considerable urging he could sometimes be persuaded to speak, but his conversational stream was meager in amount and for the most part irrelevant. On July 13, 1938, 5 cc. of serum was injected intravenously, without any noticeable reaction. On July 14, 10 cc. was injected intravenously, and the usual initial flush and diaphoresis, with slowing of the pulse rate, were noted. On July 15, 15 cc. was injected, and a similar physiologic reaction was noted, but with, in addition, a change in the behavior of the patient. He responded readily to questioning by the nurses, but the content of his replies was often irrelevant. On July 16, 20 cc. was injected, and the pulse dropped to 52 beats per minute. At no time during the course of treatment did a rise in temperature occur. The behavior improved, and the patient became cooperative.

He expressed the desire to go home and return to work. On July 18, 20 cc. was injected again; steady improvement took place, and the patient was discharged from the hospital on July 28. He returned on August 1, unaccompanied, and reported that he was feeling well; he gave a complete and relevant account of his activities since returning home. He displayed a normal degree of interest, was desirous of obtaining work and consulted with a social worker in an effort to elicit help in obtaining employment. In discussing his illness, he expressed himself in the following manner: "I must have been off my mind to act that way." At this visit he reported also that he was attending manual training classes at night, and that he had visited several employment agencies and answered numerous advertisements in an effort to obtain employment. He was advised to continue treatment and to come to the hospital at weekly intervals; at this time 20 cc. of serum was injected.

A social service investigation of the patient's home environment disclosed that it was far from happy. His mother had recently died, and the father, with whom he lived, was a hard working, none too intelligent foreigner, who constantly upbraided the patient for his inability to obtain employment. About one month after the patient's discharge from the hospital he expressed suicidal ideas, saying: "What's the use, I can't get work; I'm no good." At this time the Works Projects Administration project closed, and the father reprimanded him severely for not being able to obtain other work. The patient was also considerably shaken by the unexpected death of a close friend. He was readmitted to the hospital and was found to have regressed to his former psychotic state, exhibiting essentially the same symptoms as on his first admission.

At this time considerable difficulty was encountered in obtaining a sufficient supply of fresh blood serum from persons who had been burned. Serum a number of weeks old invariably produced severe systemic reactions in the form of chills, followed by a rise in temperature, so that its use was precluded. Because of these difficulties efforts were made to isolate the agent or agents that may have been responsible for the favorable change in behavior in the patients under treatment.

A review of the literature on toxemic manifestations associated with burns revealed no unanimity of opinion as to the exact factors responsible.

Wells (Wells, H. G.: Chemical Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1920, page 573), citing Kutscher and Heyde as early as 1911, mentioned methyl guanidine as a substance that is regularly eliminated in the urine of persons who have been burned. This substance, when injected, produces effects similar to those caused by injections of toxic urine in cases of burns.

Guanidine (imidourea, $NH:C\ [NH_2]_2$) is related to creatinine and arginine; its physiologic effects are more striking than those of other nitrogenous metabolites. These include elevation of blood pressure, slowing of respiration, decrease in pulse rate and hypoglycemia. Larger concentrations in the blood stream produce nausea and vomiting; diarrhea; marked salivation; nervous irritability; fibrillary tremors; convulsions; circulatory disturbances, e. g., peripheral vasodilatation, and increased activity of sweat glands (Major, R. H., and Weber, C. J.: *J. Lab. & Clin. Med.* **15**:125 [Nov.] 1929. Von Frank, E.; Stern, R., and Nothmann, M.: *Ztschr. f. d. ges. exper. Med.* **24**:341, 1921. Minot, A. S., and Dodd, K.: Guanidine Intoxication, *Am. J. Dis. Child.* **46**:522 [Sept.] 1933).

It is generally accepted that the normal values for guanidine concentration in the blood stream of normal human subjects is from 0.35 to 0.45 mg. per hundred cubic centimeters. These values are relatively the same as those encountered in dogs (Minot, A. S.; Dodd, K., and Riven, S. S.: Use of Guanidine Hydrochloride in Treatment of Myasthenia Gravis, J. A. M. A. **113**:553 [Aug. 12] 1939).

In 1918, Koch expressed the opinion that the essential feature of parathyroid deficiency is intoxication due to accumulation of guanidine bases. The cause of parathyroid tetany is guanidine intoxication of the central nervous system and myoneural junctions. A mother substance from which the guanidine is formed is called cyanamide, a body which may be recovered in methylated form from the

urine of parathyroidectomized dogs (Koch, W. F.: *M. & S. J. St. Louis* **2**:9, 1918). Major and Weber found that the administration of calcium in suitable amounts protects the organism against guanidine intoxication. These observations have been verified by other workers (Burns, D., and Sharpe, J. S.: *Quart. J. Exper. Physiol.* **10**:345, 1916. Koch, W. F.: *J. Biol. Chem.* **12**:313, 1912).

The hypoglycemic effects of increased concentration of guanidine in the blood stream have been investigated. Its use as a therapeutic agent in diabetes mellitus was tried both in Europe and in the United States (von Schuler, B.: *Klin. Wchnschr.* **16**:1113 [Aug. 7] 1937. Anticoman Not Acceptable for N. N. R., report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **108**:1799 [May 22] 1937). It was found to be effective when given by mouth in cases of mild diabetes mellitus (von Schuler, B.: *Klin. Wchnschr.* **17**:77 [Jan. 15] 1938). However, in more severe forms, with high blood sugar values, the dose of guanidine was necessarily high, and several cases of toxic hepatitis occurred. No permanent damage to the liver took place and the hepatic disability ended with the discontinuance of the drug (von Maier-Weinertsgrün, D.: *Deutsche med. Wchnschr.* **63**:1400 [Sept. 10] 1937). It was found, in the hypoglycemia produced by guanidine, that calcium salts are more effective in returning the blood sugar level to normal than the administration of sugar itself (Watanabe, C. K.: *J. Biol. Chem.* **33**:253, 1918; *ibid.* **34**:73, 1918. Minot, A. S.: *J. Pharmacol. & Exper. Therap.* **43**:293 [Oct.] 1931).

The convulsive and hypoglycemic effects of guanidine suggested its possible use as a so-called shock agent in schizophrenia. The physiologic effects of this drug on the human organisms, especially on the autonomic nervous system, resemble in many respects the changes witnessed during insulin and metrazol therapy. In addition to insulin and metrazol, histamine, a protein spit product and a probable factor in toxemia due to burns, has been employed, and favorable therapeutic results have been reported.

It was thought that if a substance could be found that would effectively alter the physiologic state of the organism in a manner similar to insulin, metrazol and other shock agents, but without production of coma or convulsion, a therapeutic advance would be accomplished. With this in view, experimental procedures were carried out on dogs in an effort to determine the various physiologic effects produced by varying doses of methyl guanidine. An effort was made also to determine with what degree of efficiency the symptoms produced by the drug could be controlled by appropriate doses of calcium salts.

Dog 1, weighing 24 Kg., was given 10.5 cc. of a 10 per cent solution of methyl guanidine sulfate intravenously—approximately, 43 mg. per kilogram of body weight. The dog became apprehensive and moderately restless; respirations were somewhat irregular, with short periods of apnea; salivation and increased capillary flow at the site of the wound occurred. After ten minutes, 30 cc. of calcium gluconate was injected; in a short time respirations returned to normal and the animal became less restless and apprehensive. Within fifteen minutes the dog resumed its former quiet, cooperative state and was able to walk to the cage.

Dog 2, weighing 18 Kg., was given 13.5 cc. of a 10 per cent solution of methyl guanidine sulfate intravenously—75 mg. per kilogram of body weight. Immediately after the injection, in addition to the symptoms shown by dog 1, there occurred generalized muscular tremors and occasional local convulsive-like muscular contractions. There was also incontinence of urine. In approximately ten minutes 20 cc. of a 10 per cent solution of calcium gluconate was injected intravenously, with prompt amelioration of all the signs. Within fifteen minutes the dog appeared entirely well and returned to its cage.

Dog 3, weighing 20 Kg., was given 100 mg. of methyl guanidine sulfate per kilogram of body weight. The immediate response was the same as that in the 2 preceding dogs; shortly afterward a severe generalized convulsion occurred, following a pattern of clonus, tonus and then clonus. During the seizure there

was incontinence of both urine and feces. During the end phase of the convulsive attack (clonus) 30 cc. of a 10 per cent solution of calcium gluconate was injected, and no further convulsions occurred. However, the dog was listless and did not respond to painful stimuli; it was carried to the cage, where it maintained the listless behavior for approximately two hours and then slowly became more alert; within four hours after the injection of calcium gluconate it had seemingly recovered.

Large doses (up to 370 mg. per kilogram of body weight) of methyl guanidine sulfate were injected in several other dogs; in each case the convulsions and other symptoms were controlled by injections of calcium gluconate, approximately from 20 to 30 cc. of a 10 per cent solution being required.

These experiments enabled us to establish doses that would produce varying degrees of physiologic change, up to a generalized convulsions. Further, the value of calcium salts in neutralizing these physiologic upheavals in a specific manner seemed to be demonstrated.

We are now studying the effects of methyl guanidine sulfate on various organs of the body when administered over a prolonged period. In addition, observations are being carried out on the changes in the pressure and chemical constituents of the blood that may result while the drug is being administered. We hope that our experimental work with methyl guanidine sulfate will stimulate interest in this and other chemical agents that may have a therapeutic effect in mental disorders without the production of coma or convulsion.

DISCUSSION

DR. L. J. MEDUNA, Chicago: I am glad to hear this paper, which I consider the first step forward since discovery of the shock therapies. I may remind you of the meeting in Switzerland in 1937. This was the first occasion on which a number of specialists talked over the new treatments of insulin and metrazol. As I have said, the chief aim is to find and investigate the physiologic and biochemical features of new treatments, in order to avoid the coma of insulin therapy and the seizures of metrazol therapy. There are no reasons to seek and find new convulsants, but there is necessity to find a new kind of therapy which may give the same changes that are caused by means of coma and fits. It seems to me that guanidine has a great advantage, in spite of being a convulsive drug, though in the dose administered it is not convulsive. One must be careful, however, for the effect of guanidine is not clear. After administering guanidine one sees in the patients many biochemical features which are common to the effects of both insulin and metrazol; for instance, one sees a decrease of the calcium and of sugar of the blood and a decrease of acid excretion. On the other hand, increase of blood phosphorus and blood acidity occurs, and, at least histopathologically, acute and subacute guanidine poisoning give a typical picture of myelitis, similar to that of infectious encephalitis.

The many possibilities of this new kind of treatment are not known, but I am sure that it should be investigated further.

DR. FRANCIS GERTY, Chicago: I have followed this work for the past year and know that it has been done carefully. All are anxious to know whether anatomic destruction, psychologic shock or chemical change is responsible for the supposed curative effects of so-called shock treatments. The authors are wise to proceed carefully and slowly, not jumping too far ahead in determining which of these factors is responsible for improvement in the treated patients.

DR. LEO KAPLAN, Chicago: We are at present endeavoring to study, as Dr. Madden pointed out, the effects on the organs of the body, particularly the liver and brain. We are using a dose so small as to prevent the possibility of toxemia. We are also making further clinical studies on the blood in regard to calcium and phosphorus, sugar, nonprotein nitrogen and other constituents. At present we are treating a series of patients, and the results are promising.

RALPH C. HAMILL, M.D., *Vice President, in the Chair*

Regular Meeting, Jan. 4, 1940

ALCOHOL AND THE AUTOMOBILE DRIVER: A SYMPOSIUM

The Problem as Viewed by the Chemist. DR. THEODORE E. FRIEDEMANN, Professor of Chemical Bacteriology, University of Chicago.

The Problem as Viewed by the Psychiatrist. DR. DAVID B. ROTMAN, Director, Psychiatric Institute of the Municipal Court of Chicago.

The problem of alcoholism, even if divorced from the complicating factor of the automobile, has remained baffling, even to psychiatrists. The automobile has added only another element of complexity and has become an inextricable part of the American scene. The automobile fills some fundamental needs. Its utilitarian aspects are, of course, axiomatic. That it answers an esthetic need cannot be questioned, but its psychologic implications go even deeper. Somehow, driving engenders and unleashes a terrific psychodynamic force. This explains, perhaps, the great difficulty encountered in statutory regulations of motorists. Financial responsibility features are present in the statutes of only 21 states. Feebleminded and insane persons are barred from licensure in only 18 states; idiots, imbeciles and epileptic persons, in only 16 states; habitual drinkers and drug addicts, in only 25 states. Only 12 states require examinations for eyesight, and only 2 states, for hearing. In 1938 only 14 states actually required driver's tests.

In 1939 Illinois for the first time introduced a driver's test, which is adequate as far as it goes, but could and should include a short medical, neurologic and psychiatric examination. This examination should be modeled somewhat after those employed in recruiting during the World War.

It has long been recognized that drinking involves an escape mechanism for antisocial tendencies. Speed is also an escape mechanism. The combination of the two in the same person can tend only to emphasize the personality quirk. Since 1931, in the Psychiatric Institute of the Municipal Court there has been a steady increase in the alcoholic load. Of 18,034 persons examined, 4,255 (23 per cent) were found to be alcoholic. During the first eleven months of 1939, of 2,039 cases, the offense was of alcoholic origin in 604, which represents a peak of 29 per cent. In 64.2 per cent of all cases in which drivers were referred for examination alcoholism was a strong factor. It should always be borne in mind, however, when studying alcoholic persons that often the focus of attention is on alcoholism because it offers a simple etiologic factor. Statistics from the Municipal Court show that of 64.2 per cent of persons classified as ostensibly alcoholic after careful psychiatric scrutiny, only 12.2 per cent had a condition finally diagnosed as chronic alcoholism. The remaining diagnoses are those appearing in any group of concentrated psychiatric material: dementia praecox, manic-depressive psychosis, epilepsy, dementia paralytica and feeblemindedness.

As to the validity of the chemical test, it may be hoped that the drunkometer proves itself by rigorous scientific investigation to be worthy to take its place beside the clinical thermometer and the sphygmomanometer. Its use must be limited to the time of arrest. It is by no means to supplant medical, neurologic, psychiatric and psychologic tests, which can detect symptoms long after the alcohol has evaporated. It would be as unscientific to divorce the drunkometer findings from the clinical picture as to study the spinal fluid apart from the conduct of persons from whom it was taken.

The Problem as Viewed by the Psychologist. DR. AGNES A. SHARP, Chief Psychologist, Psychiatric Institute of the Municipal Court of Chicago.

Clearly, from the psychologic point of view a drunken man is sick, not criminal. He needs "the cure," not jail, for prison does not cure him—as every magistrate

can bear witness. The judge, who should function as the educational agent of the public, does not have available the cumulative record of past experiences, individual tendencies and measures of skill and aptitudes typical of the sound educational procedures which characterize progressive work. He should know concerning the accused driver: (1) the previous driving experience and the skill which he has acquired by that experience; (2) the previous accident record, which should accompany him when he moves from state to state; (3) the motives, ascertained from all sources available—for example, the social and business drinking demands of the driver's work; (4) the degree of recklessness, as measured by public complaints; (5) the usual speed at which he actually travels (objective measures by speed determiners can be made) and (6) the driving habits. These are a part of the cumulative records and are ascertained from public complaints of other motorists and traffic officers, and from records of court disciplinary actions.

With such assistance at hand, the judge is able to act as an automobile driver clinician to the public.

The enforced isolation of the driver of an automobile requires an adaptation of men's habits that is more than a one generation achievement. This may necessitate licensing for travel only those with the peculiar constitution able to withstand aloofness from the world, as is now done for the drivers of locomotives and airplanes. Occupation, after sex, is probably the most significant primary factor by which one can classify present day mankind. No other is so important from the standpoint of income. No other is so important from the standpoint of cultural ideas, attitudes, activities and observance of the law.

In the work in the Psychiatric Institute of the Municipal Court, by a standardized road test, attitudes in driving, skill and habits are determined. It is possible to learn a man's attitude toward drinking and driving by questioning him after an accident in which drinking was involved as to how the accident might have been prevented.

Psychologic tests and equipment are now used to a limited extent in traffic clinics in Wichita, Kan., Detroit and the Psychiatric Institute of the Municipal Court of Chicago. In this institute tests of deterioration are being used in evaluation of impairment resulting from prolonged alcoholism.

Experts must compile the findings, infer the causes needing correction and codify principles for legislation, if any are necessary. Legislation is only one of many, and incidentally one of the least effective, technics for inducing desired social behavior of people.

The most promising organization, probably, would be that of a well endowed research bureau, manned by scientists who, after a careful survey, would outline the several responsibilities in the whole program to be assumed by such professional persons as physicians, chemists, penologists, psychologists, educators, sociologists, publicists, state health commissioners, city-planning commissioners, police department officers, automobile designers, highway engineers, statisticians, legislators and judges. Cooperative research has accomplished much in the study of cancer. Safety must be conceived of as a problem not soluble by a panacea.

In accident prevention programs it would seem better psychologic technic to emphasize proper driving habits; to encourage the periodic self inspection of driving habits; to use rewards rather than penalties; to direct attention to specific faulty practices. Safety needs to be sold to the world according to the same psychologic recipe as any other public commodity or service — for example, education.

The Problem As Viewed by the Law-Enforcing Officer. MR. F. M. ANDREWS, Chemical Test Officer, Evanston Bureau of Accident Prevention.

With the idea in mind that alcohol is a large factor in automobile accidents, the Northwestern University Traffic Safety Institute, in conjunction with the police department of Evanston, Ill., set out to make two series of tests, the first of which was conducted over a period of three years in the two hospitals located

in Evanston. During this time tests were made on 270 drivers involved in automobile accidents in which there were personal injuries. Through cooperation of the drivers a good cross section was obtained. It was found that 47 per cent of drivers involved in accidents resulting in personal injury had been drinking; 25 per cent of drivers so involved had more than 0.1 per cent, and 14 per cent more than 0.15 per cent of alcohol, by weight, in the blood.

A second series of tests was made to determine the percentage of drinking among all drivers, or, in other words, to establish a control group. These tests showed that 12 per cent of all drivers on the road had been drinking; 2 per cent of all drivers had more than 0.1 per cent of alcohol, by weight, in the blood (enough to affect most persons), and about 1 driver in every 250 had more than 0.15 per cent of alcohol, by weight, in the blood.

The value for the nondrinking driver being taken as 1, correlation of the figures for the two tests shows that if there is more than 0.15 per cent of alcohol, by weight, in the blood, a man is fifty-five times as liable to be involved in an accident resulting in personal injury as a nondrinking driver; if there is from 0.11 to 0.15 per cent of alcohol, he is fifteen times as liable; if there is from 0.07 to 0.11 per cent of alcohol, he is five times as liable, and if there is from 0.01 to 0.07 per cent of alcohol, he is three times as liable.

The peak in the number of alcoholic drivers on the basis of traffic flow was between 10 p.m. and 4 a.m., the highest point occurring between 1 and 2 a.m. At this time about 50 per cent of all drivers had been drinking, except on Saturday night and Sunday morning, when the rise began at about 9 p.m. and rose sharply until 12 midnight, when it reached about 75 per cent of all drivers; that figure remained the same until about 4 a.m., when it dropped to about 30 per cent and then tapered off to zero at 2 p. m. Sunday afternoon. Comparison of this curve with curves for accident drivers who had been drinking reveals a striking similarity. On a graph for the alcoholic drivers, the peak was reached from 4 to 6 a.m., when the percentage was almost 100 per cent. In determining the ages of those drinking, it was found that 28 per cent of the drinking drivers in the control group were between the ages of 25 and 30, and that the percentage then gradually declined to the age of about 60. The extreme upper and lower limits could not be accurately determined, owing to the small number of youthful and elderly drivers tested. Since there are many more men than women drivers, the percentage of women drivers seems to be much smaller, but when the figures are presented on the basis of the percentage of drinking according to the hours of the day there is little difference between the curves for men and those for women.

After a complete survey of the facts determined in the two studies, the following conclusions were reached: 1. The highest percentage of drinking drivers occurs in the early morning hours and over week ends. 2. The largest number of drinking drivers occurs in the early evening and over the week ends. 3. The peak age for drinking drivers is from 25 to 30 years. 4. Women drink and drive as much as men when the number of women driving at the various hours of the day is considered. 5. The percentage of drinking drivers involved in accidents in which there are injuries varies as does the percentage of drinking drivers. 6. As alcohol increases, accidents increase, and at a rate that is somewhat proportionate to the increase in alcohol in the blood. Finally, while, this study has not conclusively proved how important a causative factor alcohol is, the data point only in one direction: They prove more thoroughly the belief that alcohol is the no. 1 public enemy of traffic safety.

The Problem As Viewed by the Judge. THE HON. HARRY H. PORTER, Chief Justice, Municipal Court of Evanston, Ill.

In 1936 the National Safety Council appointed a committee of 23 members to study the relation of alcohol to traffic accidents. This committee was composed of enforcement officials, safety directors, medical men, toxicologists, insurance men and others, drawn from as far east as Burlington, Vt., as far west as Los Angeles,

as far north as St. Paul and as far south as Dallas, Texas. The committee was given this mandate: "Investigate as thoroughly as possible the relation between the use of alcohol and traffic accidents, and if you find that a substantial problem exists, do something about it and do it as quickly as you can."

Statistics bearing on the relationship of alcohol to traffic accidents were gathered from 48 states. Percentages varied so widely from state to state and from locality to locality within the states that it was impossible to form any accurate picture in actual figures. When the true and accurate figures are available, it will be found that the use of alcohol at the wrong time and place is responsible for from 40 to 60 per cent or more of all fatal accidents. Nearly all the members of this committee are in agreement with regard to this problem. If this estimate is true, the use of alcohol at the wrong time and place is the no. 1 major problem in combating deaths and personal injuries on the highway.

This work is solely concerned with public safety. How much people drink or whether they drink is no concern of the Council. Its problem is simply to assist in educating the driving public that the operation of motor vehicles must be completely and finally separated from the use of alcohol in any form.

The really dangerous driver is the man who has had a few drinks and is thoroughly convinced of his own sobriety and of his unequaled driving perfection—the man who insists that he is a better driver while in this condition than when he is completely sober. This driver is now called the "drinking driver." He is not recognized by the average police officer or layman as being under the influence of alcohol, because he does not manifest the outward symptoms of drunkenness in sufficient degree. This driver is the killer. The problem before the enforcing authorities is to recognize, apprehend and incarcerate drivers of this type with the utmost possible expedition.

It becomes necessary to understand the meaning of the phrase "under the influence of intoxicating liquor." One definition read: "The expression 'under the influence of intoxicating liquor' covers not only all the well known and easily recognized conditions and degrees of intoxication, but also any abnormal mental or physical condition which is the result of indulging in any degree in intoxicating liquors, and which tends to deprive [the driver] of that clearness of intellect and control of himself which he would otherwise possess. If the ability of the driver of any automobile has been lessened in the slightest degree by the use of intoxicating liquors, then the driver is deemed to be under the influence of intoxicating liquor. The mere fact that the driver has taken a drink does not place him under the ban of the statute unless such drink has some influence upon him, lessening in some degree his ability to handle said automobile." This definition was recommended by the committee to be used as a standard. A short definition for "under the influence" might be "subintoxication."

It is well known that alcohol affects the lower extremities more quickly than the hands and arms, and therefore, one may observe the toxic state in the pedestrian much more readily than in the man who sits behind the wheel. His feet seem to get "mixed up" on the pedals; they do not obey the impulses sent from the brain, or rather, perhaps, the brain is not clear on which impulses it desires to send to the extremities. His throttle foot becomes "heavy." He becomes more or less self centered and introspective, and lives for the moment in a little world of his own; at least his own desires and wishes become of paramount importance. He does not feel like shifting gears or slowing down. He tries to pass other cars and usually succeeds because the sober drivers give way. But all "the king's horses and all the king's men" cannot change the position of road curves, telephone poles, fences and railway crossings often or quickly enough to meet the changing intentions of the driver who is "under the influence" of alcohol.

There are today five well known tests for determining the degree of intoxication from which a human being suffers. These, in order, are the spinal fluid test, the blood test, the urinalysis, the saliva test and the breath test. The first two, namely, the spinal fluid and the blood test, are extremely accurate; however, in

enforcement work there are objections to their practicability. First is the difficulty of administering the test; the services of a skilled physician are necessary, and one cannot always be available at the scene of an accident or immediately thereafter. Second, there is a constant danger of infection of the subject, with a consequent prolific source of lawsuits against municipalities employing these tests. At present the most practical of these tests seem to be the urinalysis, the saliva test and the breath test. These permit a diagnosis of the amount of alcohol in the blood without penetration of the human body.

From thousands of experiments on living human beings and on cadavers, medical men and toxicologists have discovered and verified the fact that there exists an almost mathematically constant relation between the amount of alcohol in the urine, saliva or alveolar breath and the amount of alcohol in the blood; further, that there is an almost mathematically constant relation between the alcohol content of the blood and that of the brain. Therefore one is able, by ascertaining the amount of alcohol in the urine, breath or saliva, to predict with extreme accuracy the amount in the blood. This is important because alcohol in the brain means intoxication, and if one knows the alcohol content of the blood one knows the alcohol content of the brain.

It is not the alcohol in the stomach which intoxicates; it is the alcohol taken into the stomach which eventually finds its way into the blood and from the blood to the brain which intoxicates a man. Thus, it follows that it is possible for a man who has taken a smaller amount of alcohol into the stomach than another to have, nevertheless, a higher percentage of alcohol in the blood. Ordinarily, the accustomed drinker has a slower rate of absorption than has the novice. The novice, then, will usually show on test a higher percentage of alcohol in the blood than will the accustomed drinker, even with ingestion of a lesser quantity of alcohol. Furthermore, the rate of absorption of a human being varies from day to day with his condition, so that any one who thinks that he can determine his "safety point" by use of the tests is destined to be disillusioned.

Medical men and toxicologists have fixed the percentage of alcohol in the blood at and above which one may consider any person as definitely under its influence. The upper limit, at and above which any one is, for the purposes of enforcement, to be considered as definitely "under the influence" of alcohol, was fixed as 0.15 per cent of alcohol, by weight, or 1.5 parts per thousand parts of blood. This figure is liberal. The lower limit, below which no one is to be considered as "under the influence" of alcohol was fixed as 0.07 per cent. Persons showing an alcohol content of the blood between 0.07 and 0.15 per cent were to be prosecuted or not as the objective symptoms dictated. By thus standardizing the proposition of who is and who is not under the influence of alcohol, something definite and concrete has been achieved, and guesswork has been eliminated. This has, for the first time, made possible a standarized prosecution for this dangerous offense. All men may now be judged by a uniform rule.

These tests as quickly acquit the innocent as they convict the guilty; they are no respecter of position or influence or of the lack of either. They are foolproof and accurate, and have long since passed their experimental stage. Their verdict is final.

DISCUSSION

JUDGE J. M BRAUDE, Chicago: Thus far, nothing has been said concerning body tolerance and the use of alcoholic beverages. The figures which have been laid before the society mean nothing themselves except insofar as they are related to individual persons; unless steps are taken to determine on a scientific basis what the body tolerance of a particular person is, the actual amount of alcohol found in the body tissues at a particular time will have little or no significance in determining whether or not that person can be said to be under the influence of alcoholic liquor at the time the investigation or the examination was made.

Dr. Carlson inquired why the authorities have permitted him to drive an automobile without having first subjected him to an examination to determine his

driving ability. While it is true up to a certain point that the more one drives the better driver one becomes, it is also true that the times comes when one may have driven too long and that from this point one may become a poorer driver. Some of the best drivers are young people, who react to stimuli more readily than persons whose muscles and arteries have lost flexibility with age and who have poor coordination of nerves and muscles.

Illinois was one of the last states to adopt a driver's license law. Many efforts in the past to pass such legislation met defeat, until the present law was enacted about a year ago. In order to have the law passed at all, it was necessary that certain concessions be made. If concessions had not been made to those who had been driving automobiles for many years, and which exempted such drivers from the necessity of having to submit to tests and examination, it is doubtful whether the law would ever have been passed. It is almost universally true that when new legislation is adopted which licenses a particular group, it exempts from the necessity of examination those who up to the time of the passage of the new law were engaged in doing specifically those things which the new legislation undertakes to license.

I wish these tests for the determination of the alcoholic content of body fluids were in general use in Chicago. I have used them myself to advantage. I like the drunkometer not so much because it enables one to obtain the evidence which results in the conviction of a defendant, but because of the psychologic effect which it has on those who might otherwise feel they could lie their way out of a charge of drunken driving. With present methods, after a person takes a drink one may smell the alcohol on his breath, and yet the alcohol may not have had time to make its way into his blood. Without the use of a breath test a person under such circumstances may be found guilty of driving under the influence of intoxicating liquor. With use of this scientific equipment, which discloses the absence of alcohol in his breath and hence in his blood, he would be entitled to an acquittal. With the scientific tests which have been suggested this evening, much of the guesswork would be taken from the court. If it were to become generally known that a man could not lie his way out of court and that his body itself might give testimony for or against him, it might produce the effect of eliminating persons who would otherwise take the chance of driving an automobile after having imbibed alcoholic liquors; its psychologic effect would be prophylactic.

I think that there ought to be a change in some laws. It is made a crime today, under the liquor control law, to sell or dispense liquor to a drunken person or to a minor. I advocate an additional provision that would prohibit the sale, serving or dispensing of alcoholic liquor to a person while that person is in an automobile; I might even go so far as to include prohibition of the sale or dispensing of liquor for consumption on the spot if it is known or can be shown that such person is about to drive a car. Recently, the Attorney General of Illinois handed down an opinion to the effect that there is no law on the statute books which prohibits "curb service" as far as alcoholic liquors are concerned. I think that should be changed.

Dr. Sharp said that I called to her attention a situation with reference to painters which seemed to indicate that a substantial proportion of those brought into the Safety Court charged with operating motor vehicles while under the influence of alcoholic liquor were painters. I tried to find out why it was that painters, more than any other group, should get into this kind of trouble. Some persons suggested that the cause might lie in the obnoxious odor of the turpentine in the paint, which the alcohol in liquor might tend to "wash" away. However, I finally hit on what I think is the real reason. Painters usually are through work at 3 p.m.; therein, I think, lies the answer. Dinner, as a rule, is not served at home until 6 p.m. That gives them three hours within which they have nothing to do. Where do they go? To the poor man's club—the tavern. I mention this because of a tendency on the part of organized labor to agitate for shorter working hours. I think most people are in accord with such a program. While urging

for shorter working hours, however, there is also an obligation to make provisions for wholesome recreation. The problem is an intricate social one.

To me it all resolves itself to this: not what shall be done with the defendant once he is in court charged with driving while under the influence of intoxicating liquor, but what can be done to keep him from coming to court in the first place.

Dr. Phyllis M. Wittman, Elgin, Ill.: For the past three years the department of psychology at the Elgin State Hospital has been carrying on an investigation of the personality and developmental characteristics of chronic alcoholic persons and of subjects in control groups. The work Dr. Sharp mentioned was the preliminary report on 100 alcoholic persons and 100 control subjects. Certain psychoanalytic hypotheses were supported in general, but not entirely, in this study. However, it was found that chronic alcoholic patients do not form a homogeneous group. This work is being continued until at least 400 subjects have been studied, in order to permit statistical analysis.

I wonder what percentage of intoxicated drivers who are arrested would be classed as "chronic" and what per cent as "normal" alcoholic persons. A review of histories of the 62 men and 6 women classified as chronic alcoholic persons now in the institution at Elgin showed only 2 cases in which patients were driving at the time of accident; there were 12 instances, however, in which the patient was the pedestrian involved in an automobile accident. It is possible, of course, that there were a large number of accidents occurring while driving which were not discovered by the questioning of the social worker. On the other hand, the drunken driver who becomes involved in an accident may be a "normal" drinker, and may even be the one who drinks only once or twice a year. This idea occurred to me because of the much greater number of accidents on certain holidays, when many persons drink who do not drink throughout the year. To the habitual drinker, New Year's Eve, for instance, is only another night on which to drink while to other persons it may be the one night in the year on which to drink. I agree with Dr. Sharp concerning the need for knowledge about the driver's previous drinking habits as well as his driving history.

Dr. David Slight, Chicago: It would be possible to rectify many aspects of the present deplorable situation if one cared to take elementary precautions. Thus, one may well ask what is done to insure that the prospective driver is free from psychopathic tendencies and habits of alcoholism. Further, what is done to check on and endorse the licenses or to withdraw driving privileges from the thousands who yearly pass through the hospitals of Chicago suffering from alcoholic psychoses? Again, would it not be reasonable if a check were made on all persons arrested for habitual drunkenness as to whether they hold driver's licenses?

Then there is the controversial question as to the methods and standards to be applied in assessing the responsibility of the person under the influence of alcohol who is charged with a driving offense or has been involved in an accident. The routine methods of having the accused repeat test phrases, walk a line or perform simple tests of coodination have long proved their uselessness. Not that they did not have value or might not have been reasonable grounds on which to assess a person's capacity for such muscular coordination. All know too well, however, that such evidence was manna from Heaven for the defense, and the details of what happens to such evidence are too well known to call for repetition. There seems little point in perpetuating such foolishness, and if the courts cannot make any better use of such forms of evidence, one should frankly set them aside and establish more satisfactory criteria.

These are available in the chemical tests so well described this evening. Of course, the argument will appear that irrespective of how much alcohol is in the blood, such and such a man has superior mental powers, or a strong will, and can still do things with an alcoholic content that spells insensibility for another man. If the chemical tests are to be beset with such argumentation, I can only suggest that one say to the allegedly alcohol-resistant person that he do his parlor or barroom tricks in private. One will then be compelled to set an average level of values

as to what alcoholic content is to be taken as equivalent to being "under the influence" of alcohol or what behavioristic criteria are to be required. The application of such criteria may be held by some to be unjustified by law or by others to be undemocratic, but it is time a solution of these problems was achieved in average use of such forms of evidence, one should frankly set them aside an destablish more satisfactory criteria.

DR. JOSEPH A. LUHAN, Chicago: I was struck by the complex social ramifications of this problem. The dilemma that has faced my associates and me in the Psychiatric Institute of the Municipal Court is this: A person is sent to us by the referring judge with the implied question: Is this man fit to drive? Will he repeat this offense at some other time? Should his driving license be canceled or suspended? I do not think enough data are available to answer the questions in the case of persons who are not obviously unfit by reason of psychosis or mental deficiency. The value, therefore, of the program at the Psychiatric Institute of psychologic testing and general psychiatric appraisal is to secure a great mass of data from which correlations may be made that will enable one to weed out persons who should not be allowed to drive a car from those who are not psychotic or feebleminded. It seems from this discussion that the most important prophylactic weapon available at present is education of people in these matters.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

E. D. FRIEDMAN, M.D., *President of the New York Neurological Society, Presiding*

Joint Meeting, Jan. 9, 1940

Cerebral Arteriography by Means of a Rapidly Excreted Organic Iodide.

DR. SIDNEY W. GROSS.

Cerebral arteriography was first described by Egas Moniz, of Lisbon, in 1927 (L'angiographie cérébrale, Paris, Masson & Cie, 1934). In his original cases Moniz used a 25 per cent solution of sodium iodide. There were so many undesirable and serious reactions that the use of this substance was given up. Moniz experimented with other radio-opaque chemicals, among them skiodan, but finally abandoned all of them in favor of colloidal thorium dioxide, which satisfies the roentgenologic requirements and relatively infrequently produces immediate reactions. However, the objections and potential dangers inherent in the use of colloidal thorium dioxide are well known. Once injected into the blood stream, the particles are picked up by the reticuloendothelial system, especially in the liver and spleen, where they remain indefinitely. There is ample evidence of the danger of thorium compounds from their industrial use.

With few exceptions, most workers in this field have shared the opinion of Northfield and Russell (Fate of Thorium Dioxide in Cerebral Arteriography, *Lancet* **1**:377, 1937), who stated that "the use of thorotrast is inadvisable unless exact diagnosis is unattainable without it."

Recently, Robb and Steinberg (Visualization of the Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Man, *Am. J. Roentgenol.* **41**:1, 1939) reported on the visualization of the chambers of the heart, pulmonary circulation and great blood vessels in man by the injection of a 70 per cent solution of diodrast into the median basilic vein. The absence of severe reactions and the rapid and complete excretion of diodrast led me to study its possibilities for the demonstration of the cerebral circulation roentgenographically.

In 7 dogs the common carotid artery was exposed, with the animal under anesthesia induced by intraperitoneal injection of sodium pentobarbital. In 5 dogs, 30 cc. of a warmed 70 per cent solution of diodrast was injected into the common

carotid artery, and roentgenograms of the skull were taken during the injection. Excellent visualization of the arteries of the injected side of the brain was obtained. In 1 dog, 30 cc. of a 35 per cent solution and in another 30 cc. of a 50 per cent solution of diodrast were used. Visualization of the cerebral circulation in dogs with the two lower concentrations was not adequate for clinical use. One animal to which a large overdose of the hypnotic had been given by error failed to recover from the anesthesia. The other dogs seemed to suffer no ill effects on recovering from the anesthesia. Two dogs were killed twenty-four hours after the injection and the brains removed. Grossly, no abnormalities were observed. Histologic examination by Dr. Joseph Globus likewise revealed nothing significant. Two more animals were killed after five days; on removal the brains appeared grossly normal, and microscopic examination showed no abnormalities. After four months the remaining dogs appeared normal as to body weight, actions and habits.

After this experience with animals the method was applied to visualization of the cerebral circulation in man. The following technic was finally devised. The patient is prepared by the administration of 5 grains (0.3 Gm.) of phenobarbital in divided doses during a period of several hours before the injection and by withholding food for the six preceding hours. About one and a half hours before the injection from 1½ to 3 grains (0.097 to 0.195 Gm.) of seconal (sodium propylmethylcarbinylallylbarbiturate) is given, and just before the injection a hypodermic injection of morphine and atropine is administered.

With the use of local anesthesia the common carotid artery is exposed at the level of the thyroid cartilage. This can be done either by a small incision along the anterior border of the sternocleidomastoid muscle or by a transverse incision in one of the creases in the skin. The bifurcation of the common carotid artery is usually opposite the upper border of the thyroid cartilage, but at times is much higher. It is easier, therefore, to inject the common carotid artery routinely, since the main current of blood will carry most of the injected material into the cerebral circulation. However, if desired the internal carotid artery may be used. This vessel is deeper and somewhat lateral to the external carotid artery. After some experience it is possible to expose the common carotid artery in a short time.

If possible, exposure of the artery and the roentgenographic procedure should be carried out in the same room. When this cannot be arranged it is necessary to transport the patient from the operating room to the roentgenographic department, since portable roentgen ray equipment is rarely satisfactory for this type of work.

The patient is placed on the roentgenographic table with the head held securely in position for a lateral exposure of the skull. The casette is in place and the technician ready to expose the film. With aseptic precautions a 30 cc. syringe is filled with a warm 70 per cent solution of diodrast. The wall of the artery is then penetrated with a curved needle, 1½ inches (3.8 cm.) in length, to which a short rubber tube is attached. Up to the present an 18 gage needle has been used. At the suggestion of Dr. Arthur Blakemore, a curved, 16 gage needle with a small cutting edge will be tried in the future.

The syringe is connected with the rubber tubing, and after it is insured that the needle is within the lumen of the artery by permitting a few cubic centimeters of blood to run into the syringe the solution is injected rapidly. When 10 cc. has been injected a signal is given and the first film exposed. The injection is continued at the same speed until about 15 cc. has been injected, and then a second film is exposed as rapidly as possible. An exposure of not more than one-fifth to one-fourth second is used, without the Bucky diaphragm. If the first film is satisfactory I have not attempted to secure a second. However, if stereoscopic films are wanted or the first exposure is not satisfactory, the remaining 15 cc. of solution is injected. The needle is then withdrawn from the artery and the wound sponged with warm physiologic solution of sodium chloride. Bleeding usually stops at once, though in some cases slight pressure for a few minutes facilitates this. The wound is closed with a few silk skin sutures.

The foregoing procedure has been carried out in 10 cases. During the injection the patient's skin may become flushed and there may be a rise in blood pressure of from 20 to 40 mm. After a minute or two profuse persipration, nausea and vomiting may occur. Three patients had mild jacksonian convulsions, beginning in the contralateral upper extremity and lasting thirty to sixty seconds. Since this experience, every patient is prepared by the administration of barbiturates before the injection.

In 1 case the intracarotid injection of a 70 per cent solution of diodrast may have had some relation to the subsequent development of hemiplegia. The patient was a woman aged 42 who had had severe headaches for several weeks before admission to the hospital. On the morning of her admission she complained of intense headache. She suddenly had a convulsion and became comatose. The left pupil was dilated, the reflexes were all increased and the blood pressure was 150 systolic and 85 diastolic. Spinal puncture yielded grossly bloody fluid. Two days later the patient was somewhat more alert. There were rigidity of the neck and ptosis of the left eyelid. As consciousness returned she complained of diplopia. Eighteen days after the acute ictus the patient seemed to be in good condition and an arteriogram was made with the patient under anesthesia induced by avertin with amylene hydrate. She had a slight convulsion on the right side, lasting about thirty seconds, but was returned to the ward in good condition. Two days later there developed high fever, and pneumonia involving the lower lobe of the right lung was found. She became comatose, and right hemiplegia was noted. She gradually improved under therapy with sulfapyridine and oxygen. The weakness in the lower extremity improved, but aphasia and paralysis of the right upper extremity persisted. The arteriogram in this case showed an increase in the number of blood vessels in the left posterior temporal and parietal regions. Such increased vascularity is indicative of a glioma or other vascular neoplasm. Unfortunately, consent for operation was not obtained, and the patient died without verification of the lesion.

The following precautions should be observed in using diodrast for intracarotid injection: 1. It should not be employed with patients having severe hepatic disease, nephritis or hyperthyroidism. 2. The 70 per cent solution of diodrast must be clear at the time of injection. If care is taken to keep the solution at 37.5 C., crystallization can be prevented. 3. Leakage of the radio-opaque solution should be avoided, since spilling of any hypertonic solution into the tissues may result in irritation. 4. The solution must not be injected until the operator is convinced that the point of the needle is within the lumen of the artery. 5. Caffeine and epinephrine should be on hand for rapid injection in case of severe reaction.

Cerebral arteriography is indicated when accurate diagnosis is not possible by other methods. It should find its greatest usefulness in the diagnosis of intracranial aneurysms and vascular anomalies of the brain.

DISCUSSION

DR. CORNELIUS G. DYKE (by invitation): I appreciate the attempts of Dr. Gross to obtain a substance which will be innocuous and which will satisfactorily visualize the cerebral vascular tree. As Dr. Gross has said, the substance which he has used is rapidly excreted by the kidneys. In 1 of the cases at the Neurological Institute in which diodrast was injected into the common carotid artery, a roentgenogram of the abdomen and pelvis showed the dye in the bladder and pelves of the kidneys thirty minutes later. My experience in the use of the drug is limited to 3 cases.

In a man aged 51, whose main complaint was violent convulsive attacks, a plain roentgenogram of the skull showed enlargement of the sella turcica, with destruction of the left anterior clinoid process. The possibility of the lesion being an aneurysm had, therefore, to be considered, although a pituitary adenoma was the more likely lesion. Gas encephalograms failed to give any additional information as to which of the two lesions was present, and therefore an injection of

diodrast was made. On Dec. 13, 1939, 20 cc. of a 70 per cent solution of diodrast was injected into the left common carotid artery, but owing to technical difficulties in the timing of the injection and the roentgenographic exposure, we were able to visualize only a small amount of the vascular tree, namely, the sylvian vessels. Therefore, it was decided to repeat the procedure two days later. Dr. Arthur Blakemore, who has performed the operative portion of the test in all 3 cases, exposed the left common carotid artery a second time and found it completely thrombosed. He was unable to withdraw any blood from it, and the injection could not be repeated.

On the same day a second patient was examined. A woman aged 29 complained of hypesthesia and dysesthesia of the entire left side of the body, which had been progressive for two years, weakness of the left arm and leg, convulsive attacks for two years and, lately, a throbbing headache in the right frontal region. Neurologic examination disclosed 1 D. of papilledema in each eye; the right pupil was larger than the left, and there was weakness of the left side of the body; a bruit was present over the right eyeball. Roentgen examination of the skull showed definite atrophy of the posterior clinoid processes and dorsum sellae, and the floor of the sella turcica was lower than usual. An arteriogram was made with the injection of 20 cc. of a 70 per cent solution of diodrast. The internal carotid artery coursing along the sella turcica through the cavernous sinus, the middle cerebral artery and the sylvian vessels were visible. In addition, a large mass of opaque material had collected along the posterior limb of the sylvian fissure and in the posterior parietal region. The veins and arteries were filled with the dye, so that the examination gave an excellent idea of the extent of an arteriovenous angioma of the right parietal and inferior central areas. This patient had no reaction immediately or later.

The next case was that of a man aged 45 who had had acromegaly for thirteen years. For one week prior to admission to the hospital he had had extremely severe headache, and a few days before admission there developed sudden blindness in both eyes and ptosis of the right eyelid. The blindness improved somewhat in the next few days; the plain roentgenograms of the skull showed a rather thick skull, a large heavy jaw and definite enlargement of the sella turcica, indicating a chromophilic pituitary adenoma. However, because of the suddenness of the symptoms, the clinician expressed the belief that the patient might have an aneurysm, and an arteriogram was done. On Jan. 2, 1940, 35 cc. of a 70 per cent solution of diodrast was injected into the right common carotid artery, which resulted in excellent visualization of the blood vessels of the brain and the meninges and of some of the vessels of the scalp. However, immediately after the injection of the dye the patient became unconscious and had a series of convulsive jerks on the left side. He remained in coma for five days, after which he began to use his left arm and move his left leg, regained consciousness and made a slow recovery.

It is my opinion, therefore, that although a drug is available with which the vascular tree of the brain can be well visualized, it is at present dangerous to use in 70 per cent concentration. As Dr. Gross has said, the solution of the problem probably lies in using a concentration of diodrast of between 30 and 50 per cent. The quantity of dye injected should not exceed 20 cc. By using these two precautions I believe most of the danger in the use of the diodrast in cerebral arteriography will be eliminated. Lantern slides illustrate the cases previously mentioned.

Dr. Irvine H. Marshall (by invitation): Diodrast is the diethanolamine salt of 3,5-diiodo-4-pyridon-N-acetic acid. It has an iodine content of 49.68 per cent; it is maximally stable with 1 mol of water of crystallization, and at 37 C. a saturated solution contains 73 Gm. per hundred cubic centimeters of the anhydrous compound. Sterilized by autoclaving, it can be resterilized by boiling.

Local irritant effects of diodrast and the rate of absorption have been studied in rats, rabbits and dogs, both subcutaneously and intramuscularly. Roentgen

studies showed approximately 35 per cent absorption in twenty minutes after subcutaneous injection and complete absorption either subcutaneously or intramuscularly in from sixty to one hundred and twenty minutes. The initial rate of absorption was distinctly greater by the subcutaneous than by the intramuscular route. Local irritation after subcutaneous injection was of little significance. Following intramuscular administration there was a moderate inflammatory response. No evidence of symptomatic pain accompanied the injections. The vessels used as routes of injection in the larger animals were apparently not damaged, as many samples of blood were withdrawn after the completion of these experiments. These findings confirm and extend the clinical observations already reported in the literature.

Symptoms referable to the central nervous system followed the intravenous injection of large doses (1.5 to 3.0 Gm. per kilogram of body weight) in rats. There were an increase in respiratory rate, and with repeated doses the development of a hypertonic state, which might or might not be associated with convulsive tremors. With rabbits mild excitation and hyperexcitability were obtained for three to seven minutes after the injection of 1.5 to 2.0 Gm. per kilogram of a 70 per cent solution of diodrast. Such doses correspond to from four and six-tenths to seven times the maximal clinical doses used in man. Unanesthetized dogs (12 to 15 Kg. in weight) receiving 10 to 20 cc. of a 70 per cent solution by vein showed no symptoms. These doses have been repeated two to three times in a three hour period without evidence of intolerance.

The blood pressure, heart rate and respiratory rate in dogs given small intravenous doses showed negligible responses. Large doses produced a transient drop in blood pressure, acceleration of heart rate and increase in respiratory rate, which with maximal doses returned to normal within five minutes. Rapid injection produced transient exaggeration of the responses, which lasted about ten minutes. These observations confirm the findings of Heathcote and Gardiner. Moore and Campbell indicated the lack of significant systemic responses to intravenous injection of diodrast clinically.

The effect on isolated organs was one of hypertonicity, since the concentrations employed were outside the physiologic range.

Diodrast appears to be almost quantitatively excreted by the kidney, in largely, if not completely unchanged form. Elsom and his associates observed that excretion depends on the concentration in the plasma and suggested that the excretion curve is evidence of tubular excretion. Herbst and Baumrucker found in dogs that the four hour excretion of diodrast equaled the phthalein output for the first two hours.

The intravenous lethal dose (L. D. 60) of a 70 per cent solution for the mouse is 5 Gm. and for the rat 4.5 Gm., per kilogram of body weight. The tolerated dose for the mouse is 3.75 Gm., and for the rat 3.5 Gm., per kilogram of body weight. Acute deaths are due to respiratory paralysis. Doses ranging from the dose tolerated by man to ten times that amount have been well borne by dogs.

In summary, in view of the low toxicity, the excellent tolerance, the low incidence of severe reactions, and the high degree of excretion, the use of diodrast in cerebral arteriography is suggested.

Dr. Lawrence Pool (by invitation): I commend Dr. Gross on his excellent paper. My only excuse for taking part in this discussion is that I have had a series of 8 cases in which I carried out essentially the same procedure, but used a 35 instead of a 70 per cent solution of diodrast; in employing the weaker solution I had no unfortunate sequelae, either transient or lasting, so far as is known. All the injections were made with the use of local anesthesia, and preliminary medication of morphine and scopolamine was given shortly before the procedure was begun. In all 8 cases I injected the solution into the internal carotid artery, in none into the common carotid artery, believing that the former method would give better visualization of the intracranial vasculature. The "con-

trast" obtained with the weaker solution is not as effective as that which Dr. Gross obtained with the 70 per cent solution, but I think it worth using because the after-effects seem to be less noticeable.

I suspected that one of my patients had an intracranial aneurysm, because in the course of the last three years he had had two episodes of spontaneous subarachnoid hemorrhage. He came to Bellevue Hospital because of left homonymous hemianopia, and it was thought that injection of the dye would outline an aneurysm; if so, the internal carotid artery could be ligated. Four injections were made. Fortunately, the rubber tubing leaked a little, so that the full amount of dye was not introduced into the vessel for the first two roentgenograms. I say fortunately because a study of these two plates with Dr. Gross has shown a "puddling" effect which I believe represents a collection of dye in two small aneurysms, caused by weakening of the arterial media (the muscularis), at the points of bifurcation of the branches of the middle cerebral artery. Such a condition was described by Forbus in the *Bulletin of the Johns Hopkins Hospital* several years ago.

I gave each of the patients at least four injections at one sitting, with no noticeable effects of any kind. The pulse rate was followed closely; each patient was watched carefully and questioned closely, with no evidence as to change in vital signs or subjective complaints. In conclusion, therefore, I think the weaker (35 per cent) solution of the dye can be used without difficulty in intracranial arteriography.

Dr. Sidney W. Gross: I do not want to leave the impression that a 70 per cent solution of diodrast injected into the carotid artery is an entirely safe procedure. I tried to point out in my presentation that there were reactions during three injections. I am grateful to Dr. Dyke for the report of his cases, and to Dr. Pool for his contribution, which will make this procedure a safer one. The 70 per cent solution of diodrast was employed in dogs because adequate visualization was not obtained with 35 and 50 per cent solutions. The dog's skull and scalp are so much thicker than those of the human being that a roentgenographic technic suitable for the dog's skull is not necessarily satisfactory for the human.

In Dr. Dyke's cases the amount of 70 per cent solution of diodrast injected was excessive. Thirty-five cubic centimeters is almost twice as much as I have given in one injection. I believe that all intracarotid injections, regardless of the material injected, have some risk. A great many accidents have occurred with colloidal thorium dioxide, and hemiplegia and death have been reported to have followed its use; in addition, thorium dioxide is not excreted. I believe that the cerebral arteriographic procedure should be used only when the diagnosis cannot be made by other methods, and when a diagnosis is essential for guidance in further treatment.

Recent Experimental Studies on Functions of the Frontal Lobes. Dr. J. F. Fulton, New Haven, Conn. (by invitation).

The most notable recent advances in knowledge of functions of the frontal lobe relate to the following regions: (i) area 8, or the frontal visual field, (ii) the frontal association areas (especially areas 9 and 10), (iii) the respiratory area on the orbital surface of the frontal lobe (apparently area 12) and (iv) the face area.

Here, the old numerical designations of Brodmann have been retained, but Dusser de Barenne and McCulloch have introduced a new scheme which facilitates designation of the functional subdivisions of the arm, face, leg and other areas. Thus, F.4 refers to that part of area 4 serving the face; F.4s the part of the strip region intermediate between area 4 and area 6, which lies opposite the face area. This new shorthand is vastly superior to the former schemas, and I propose to follow it in the ensuing discussion.

Area 8.—Kennard and Ectors (Forced Circling Movements in Monkeys Following Lesions of the Frontal Lobes, *J. Neurophysiol.* **1**:45-54, 1938) and Kennard (Alterations in Response to Visual Stimuli Following Lesions of Frontal Lobe in Monkeys, ARCH. NEUROL. & PSYCHIAT. **41**:1153-1165 [June] 1939) have confirmed earlier work that stimulation of area 8 causes: (i) conjugate deviation of the eyes toward the opposite side, with a tendency toward head turning in the same direction; (ii) pupillary dilation; (iii) opening or closing the lids, and (iv) lacrimation, especially of the contralateral eye. Lesions of area 8, on the other hand, cause a conspicuous syndrome characterized by conjugate deviation of the eyes toward the side of the lesion, forced rotation toward that side during locomotor movements and "pseudohemianopia," in which the subject fails to heed objects in the opposite visual field. The effects of lesions of area 8 are transient, disappearing entirely within two to six weeks, although the forced rotation may sometimes persist for much longer periods. Control observations indicate that isolated ablation of any other part of the hemisphere does not give this syndrome. Ablation of the occipital lobes, for example, gives true hemianopia without forced rotation. When area 8 is removed from both sides, the animal for a time appears dazed and fails to respond normally to objects brought into its field of vision, and its facies become as immobile as in the case of parkinsonism. After some weeks the gaze becomes less fixed; the animal becomes restless and distractable, and thereafter permanent motor hyperactivity develops, which persists indefinitely so long as the animal is in a lighted room.

Frontal Association Areas.—The psychomotor changes observed by Carlyle Jacobsen in animals after ablation of the frontal association areas led Egas Moniz (Tentatives opératoires dans le traitement de certaines psychoses, Paris, Masson & Cie, 1936), Watts and Freeman (Some Observations on Obsessive Ruminative Tendencies Following Interruption of the frontal Association Pathways, *Bull. Los Angeles Neurol. Soc.* **3**:51-66, 1938; Psychosurgery: Effect on Certain Mental Symptoms of Surgical Interruption of Pathways in the Frontal Lobe, *J. Nerv. & Ment. Dis.* **88**:589-601, 1938; Lyerly (Prefrontal Lobotomy in Involutional Melancholia, *J. Florida M. A.* **25**:225-229 [Nov.] 1938; Transsection of the Deep Association Fibers of the Prefrontal Lobes in Certain Mental Disorders, *South. Surgeon* **8**:426-434, 1939) and others to study the effects of bilateral interruption of the prefrontal projections in man. Patients with involutional melancholia and certain other grave psychiatric disturbances have, as a result of the procedure, become euphoric, cheerful and able to conduct their lives successfully without institutional care. After such frontal lobotomies the blood pressure immediately drops, the skin of the extremities and face becomes warm and dry and with these changes in the autonomic sphere there is a profound concomitant alteration of the psychomotor status of the patient.

The Respiratory Area.—Respiration is influenced by the hypothalamus and the cerebral cortex, as well as by the medullary levels. Bailey and Bremer (A Sensory Cortical Representation of the Vagus Nerve, *J. Neurophysiol.* **1**:405-412, 1938) found on stimulating the central end of the vagus nerve that conspicuous changes occurred in the electrocorticogram of area 12 (orbital surface of the frontal lobe), and of no other part of the cerebral cortex. More recently, Bailey and Sweet, in unpublished observations, have found that respiration can be inhibited on faradic stimulation of the orbital surface of the frontal lobe. Acceleration in respiratory rate may be obtained from area L.6, as has been pointed out by Smith (The Representation of Respiratory Movements in the Cerebral Cortex, *J. Neurophysiol.* **1**:55-68, 1938), Bucy and Case (Cortical Innervation of Respiratory movements: I. Slowing of Respiratory Movements by Cerebral Stimulation, *J. Nerv. & Ment. Dis.* **84**:156-178, 1936) and others.

Face Area.—The subdivisions of the face area, originally recognized by the Vogts, have been largely substantiated by the recent studies on stimulation and ablation of this region, carried out in monkeys and chimpanzees by Walker and

Green (Electrical Excitability of the Motor Face Area: A Comparative Study in Primates, *J. Neurophysiol.* **1**:152-165, 1938). Bailey and Sweet's disclosure concerning the respiratory area, however, modifies the conclusions of the Vogts and others, that area F.6b is to be regarded as the respiratory area. Area L.6b affects respiration only when current is allowed to escape along the moist orbital surface of the frontal lobe. Dusser de Barenne, McCulloch and Ogawa (Functional Organization in the Sensory Cortex of the Monkey [Macaca mulatta], *J. Neurophysiol.* **1**:69-85, 1938; Functional Organization in the Face-Subdivision of the Sensory Cortex of the Monkey [Macaca Mulatta], *ibid.* **1**:436-441, 1938) found, on local strychninization of the subdivisions of the face area, that F.4s and F.1 suppress the electrical activity of F.4, indicating that F.4 is normally regulated by these regions. Analysis of the effects of ablating the face area led Green and Walker (The Effects of Ablation of the Cortical Motor Face Area in Monkeys, *J. Neurophysiol.* **1**:262-280, 1938) to conclude that area 4 sends direct cortical projections to the final motor neurons of the labial muscles, the muscles of the food pouches and the muscles of the tongue. Area F.6a probably has few direct motor projections, and area F.6b possesses independent projections which are mainly concerned with gross movements of the tongue, fauces and vocal cords. The facial musculature is represented almost solely on the contralateral cortex.

Fulton and Dow (Postural Neck Reflexes in the Labyrinthectomized Monkey and Their Effect on the Grasp Reflex, *J. Neurophysiol.* **1**:455-462, 1938) found that the face areas must be removed in order to demonstrate tonic neck reflexes.

In discussion, it is pointed out that all the vegetative functions which have representation in the hypothalamus are rerepresented in the frontal lobes.

DISCUSSION

DR. KURT GOLDSTEIN: My task in the discussion of this excellent paper by Dr. Fulton can be only to make comments on the findings in human beings with lesions of the frontal lobe as compared with those in animals. One must keep in mind that because the lesions are not circumscribed in man one cannot differentiate such definite symptoms corresponding with the excitation or destruction of single areas in the frontal lobes as is possible in animal experimentation. Indeed, clinical observation also reveals symptom complexes in which, in relation to more severe damage of the one or the other of the areas, one or the other group of symptoms is in the foreground.

Dr. Fulton has discussed so many phenomena observed in animals with lesions of the frontal lobe that I can take into consideration only a few. The first point I wish to stress is that vasomotor disturbances do not uncommonly occur in human beings with lesions of this part of the brain (*München. med. Wchnschr.* **44**:1249, 1917; **45**:65 and 104, 1918).

Twenty years ago I described changes in blood temperature and blood pressure and vasomotor disturbances in the hand on the side opposite lesions located directly behind the frontal lobe. All these changes appeared without any motor or sensory disturbances, and could not be considered as sequelae of spastic paralysis.

I was glad to hear that Dr. Fulton has observed tonic phenomena, head turning and increased neck reflexes—symptoms which in the literature on animal experimentation are seldom mentioned and in the description of the findings in human beings have not had the evaluation they deserve. In this respect I wish to point to several papers by myself and my co-workers (Clinical and Theoretic Aspects of Lesions of the Frontal Lobe, ARCH. NEUROL. & PSYCHIAT. **41**:865 [April] 1939). I was especially interested in what Dr. Fulton said about disturbances in the eye movements. Here, human pathology was utilized to distinguish between various groups of changes associated with lesions of the frontal lobe: A. Impairment and subjective aggravation of voluntary movement to the side opposite the lesion. In cases of these changes the lesion is located in the middle of the first frontal convolution (Bartels, M.: *Klin. Monatsbl. f. Augenh.*

42:171-188, 1919). B. Deviation of the eyes to the homolateral side. This takes place if in impairment of the movement to the other side the tonic innervation to this side is preponderant. C. So-called fixation nystagmus. If the patient tries to look to the opposite side there appears nystagmus with the slow component to the opposite side. This nystagmus is produced in the following way: The voluntary movement to the side is normally executed in antagonism to the tonic innervation of the muscles turning the eyes to the opposite side, which tonic innervation guarantees the normal performing of the voluntary movement; in diminution of voluntary innervation this tonic innervation becomes predominant and throws the eyes to the opposite side; in the performance of a voluntary movement this slow, tonic, antagonistic movement is first overwhelmed by the voluntary movement to the opposite side; because that is impaired, after a certain time the tonic movement becomes stronger; then again the voluntary movement dominates, and so on. The result of this changing of the dominance of the one or the other innervation is the nystagmus. D. Diminution of optokinetic nystagmus in the direction opposite the location of the lesion (Kroll and Minkin-Goldstein), which not infrequently is observed hand-in-hand with the lack of movement of the eyes to the one side. E. Apraxia. The eyes may be movable normally in all directions, except in one particular direction: Here the eyes can be moved by direct stimuli, i. e., by an object which the person has to follow, but they cannot be moved in this direction if the patient is asked to move his eyes voluntarily without having an object.

Dr. Richard Brickner: I agree with Dr. Goldstein that in some respects one cannot compare the results of animal and of human experimentation. This refers especially to the association areas. In another respect, the work on animals may have a direct bearing on that on human subjects and teach a great deal; these are the aspects which Dr. Fulton dwelt on tonight—the relation between the cortex and the visceral function throughout the body. In no laboratory has as much been done as in Dr. Fulton's to localize areas in the cortex, particularly in the frontal lobes, from which visceral function can be influenced. I refer to functions of the bladder, the intestine, the heart, the sweat glands, and to a number of organs and their functions besides those which he mentioned.

In everyday experience with man, including personal experience, one can often see situations in which it becomes pertinent to consider how and why some visceral functions have a cortical locus so near the place where complicated intellectual functions occur. Blushing is perhaps the best example. We, as physicians, know particularly about blushing and its relation to intellectual functions of the frontal lobe, because one of the first teachings in medical school was Osler's dictum that one must learn how to control the vasomotor system of one's face. There are various influences of ideas on bladder function, which many people experience, such as inability to urinate when any one else is in the room. Various kinds of excitement are apt to stimulate the manufacture of urine by the kidneys. One sees evidences of changed behavior in other primitive functions, such as eating, caused by cortical and often frontal cortical action. Hysterical anorexia and vomiting are common. The sexual function needs no emphasis, because all know how frequently a profoundly rooted, archaic function such as this can be disturbed by thoughts which are complex enough to be considered activities of the frontal lobe.

Certain examples may be mentioned. I may cite, first, some of the pilomotor reactions which occur in excitement and which can be elicited by certain thoughts. Some years ago I had the opportunity to observe some patients with hemiplegia. Autopsy was not performed; it stands to reason that the motor area was separated from the lower motor neuron. In these patients gooseflesh, when elicited by scratch, was no greater on the hemiplegic side than on the other, but in an emotional state there was a marked display of gooseflesh on the hemiplegic side, in contrast to little on the unaffected side. This showed that somewhere in the

brain there are cells which influence the pilomotor system, and that these cells are themselves influenced by neurons of intellect. I have had an opportunity to observe 2 patients with Raynaud's disease, each of whom had involvement of only one or two fingers. Both of these persons had blanching of the fingers in the cold, and under no other conditions, except when they thought about going out into the cold. The mere idea that they were going to go out would cause blanching of the fingers, and in 1 case holding the hand over a basin of cold water was enough to cause the blanching.

I shall cite only 1 other case in which such intellectual-somatic phenomena were shown nicely enough to illustrate the mechanism. A man complained of frequent itching of the groin, for which no local cause had been found. During conversations with this patient it developed that the itching came only when he mentioned his mother. He was allowed to talk when on the examining table, and each time his mother was mentioned there was marked movement of the dartos muscle, which by causing the hairs to move produced the itching. This patient had frank incestuous desires toward his mother. Many other examples could be given, but I have said enough to show what I mean. I think it is of great importance to consider the proximity of cortical areas for visceral function to areas for thought.

Dr. Morris B. Bender: I had the great opportunity of working in Dr. Fulton's laboratory and of observing some of the monkeys he has described in which area 8 was removed. From my own observations I found the visual defects apparent, as Dr. Fulton said. If the monkey was threatened with a menacing gesture on the side of the field of vision opposite that on which area 8 was removed there was no blinking response, whereas on confronting the monkey on the side contralateral to the uninjured area 8 the blink response was present. This lack of response is not due to a true scotoma or hemianopia, because bilateral removal of area 8 does not cause blindness. Such a monkey when allowed to run about in the hall will move along and not bump into objects. Neither is this visual defect due to the conjugate deviation of the eyes to one side, for in monkeys in which only the eighth nerve is sectioned the eyes deviate to the side of the lesion, and in these animals the apparent field defect cannot be elicited. It is my impression that the type of visual dysfunction described by Dr. Fulton is due to a disturbance in integration between the oculomotor center in the frontal lobe and the visuosensory center in the occipital lobe, the functional connection being broken in the fronto-occipital association fibers.

Dr. John E. Scarff: As a result of the observations made on 12 patients in whom either the right or the left frontal lobe had been removed, incident to the removal of tumors of the frontal fossa, Dr. Stookey, Dr. Teitelbaum and I feel justified in making certain broad generalizations regarding the functions of the frontal lobes. First, it seems indisputable that either frontal lobe separately can carry on the work originally done by the two frontal lobes, without detectable impairment of intellectual or emotional functions. Second, our observations disclose no dominance of one of the frontal lobes. Finally, we believe that the symptomatology of the frontal lobes is due not so much to suppression as to distortion of activity of these lobes. The second patient of our group is an example: A woman was unable to bring a fork to her mouth, to stand alone or to walk or find her way from one end of the bed to the other as long as a disease process was present which irritated the left frontal lobe and caused it to function in a distorted manner. As soon as this irritating factor was removed, though the entire frontal lobe was removed with it, the patient again became essentially a normal person.

We did not observe the forced turning immediately following the removal of these lobes that Dr. Fulton has described in animals.

Dr. J. F. Fulton: I am grateful for the generous response to the presentation. It is obviously impossible to discuss in detail the various points raised. I am much

interested in Dr. Goldstein's remarks concerning his observations in man on head turning and vasomotor phenomena.

Let me take up two other points which were brought up in the discussions by Dr. Goldstein and others: 1. With respect to a comparison of the results in man and those in animals, my feeling is this: If the experimental laboratories and the clinical observers could find it possible to adopt a common terminology many discrepancies would cease to exist, and the two sets of data would become less divergent; it is with this in mind that in experimental studies on monkeys my colleagues and I have deliberately adopted forms of testing that are applicable in the clinic. To cite one example, weight discrimination: It is possible for any one who will take a few minutes to discover what the patient's capacity for weight discrimination is. We have done that with experimental animals, and it is a far easier problem with the human being, who can tell what his sensations are. It is my feeling that when they are tested by common forms of investigative procedure the differences in organization of the brain of apes and that of human beings are slight; actually, we human beings differ far less from apes than some think. In the psychomotor sphere there may be larger differences, as Dr. Brickner has mentioned.

2. The other point has to do with equilibration. This may sound dogmatic, but I have never seen anything which suggests a disturbance in equilibration following a lesion of the frontal lobe, either isolated or complete. I do not know why the term "disturbance in equilibration" is used in describing the disorder associated with lesions of the frontal lobe in man. I must confess that in the few cases I have seen I have never seen anything approaching a flocculonodular syndrome.

Pupillography: Its Significance in Clinical Neurology. DR. OTTO LÖWENSTEIN (by invitation).

The pupillographic procedure is a method of recording the pupillary movements of both eyes simultaneously and under darkened conditions. Its importance is derived from two basic facts: 1. The pupillary pathways have within the nervous system enormous extensions, both sympathetic and parasympathetic, which are in connection with many upper and lower parts of the central nervous system. 2. Lesions in different parts of these pupillary paths produce characteristic modifications of the pupillary movements and reflexes, which are disclosed by pupillographic examination.

The normal types of the pupillary reflex to light are discussed: Four constitutional types exist; they correspond to four types of centrally conditioned equilibrium between the sympathetic and the parasympathetic nervous system: sympathicohypertonia, sympathicohypotonia, parasympathicohypertonia and parasympathicohypotonia.

The reflex to light, like all other vegetative functions, can be fatigued—a fact which until now had not been established. When the reflex to light or that to darkness (both of which in man are relatively independent of one another) is stimulated by successive stimuli, it can be fatigued; the pupillary reaction to light, for instance, passes through seven stages of fatigue, and then becomes exhausted. The symptoms of fatigue which one can produce by a succession of tiring light stimulations have their origin predominantly, not exclusively, in the parasympathetic paths of the reflex arc (Löwenstein, O.: Der psychische Restitutionseffekt. Das Prinzip der psychisch bedingten Wiederherstellung der ermüdeten, der erschöpften und der erkrankten Funktion, Basel, Switzerland, Benno Schwabe & Co., 1937).

The exhausted reflex to light can be restored immediately by the introduction of another sensory stimulus—a sound stimulus, a touch stimulus, a pain stimulus or even a purely psychologic stimulus. This phenomenon, called the "psychosensory restitution phenomenon," is predominantly due to a sympathetic reflex.

The reflex to darkness, the psychosensory restitution phenomenon and the psychosensory dilatation are, in the main, sympathetic reflexes. The reflex to

light, the reflex to near vision and the Piltz-Westphal phenomenon are, for the most part, parasympathetic reflexes. In the successive testing of these phenomena it is possible to examine systematically the totality of the pupillary pathways, and to distinguish between sympathetic and parasympathetic lesions, both central and peripheral.

In numerous cases of lesions of the central sympathetic system studied in collaboration with Westphal (Löwenstein, O., and Westphal, A.: Experimentelle und klinische Studien zur Physiologie und Pathologie der Pupillenbewegungen mit besonderer Berücksichtigung der Schizophrenie, Berlin, S. Karger, 1933), a form of pupillary reaction to light was found which was called "tonohaptic reaction." We found it first in cases of catatonia and postencephalitis, and later in those of manifold lesions of the diencephalon. When the tonohaptic reaction is found, whether or not it is associated with other neurologic symptoms or with indefinite neurasthenic or psychasthenic symptoms, it always gives evidence of the presence of a lesion within the diencephalon, either cicatrized or still in evolution. Cases of this reaction are often associated with the sequelae of encephalitis of early childhood, and sometimes even with an incipient tumor of the diencephalon.

The tonohaptic reaction may be associated with an increased psychosensory restitution phenomenon, with an increased reflex to darkness or with modifications of psychodilatation, all of them either unilateral or bilateral; these variations offer the means of distinguishing between central irritation and central paralysis, or peripheral paralysis within the sympathetic system.

The seven stages of fatigue are primarily conditioned by parasympathetic fatigue. In pathologic conditions these stages may exist as permanent forms—persisting for a longer or a shorter time—when the function degenerates under the influence of pathologic factors. They may be considered as incomplete forms of an Argyll Robertson symptom in evolution.

The identity of forms existing between physiologic, that is transitory, fatigue symptoms and permanent types of pathologic degeneration is called the "law of analogy between physiologic fatigue and organic degeneration of functions" (Löwenstein, O.: Les troubles du réflexe pupillaire à la lumière dans les affections syphilitiques du système nerveux central, Paris, Gaston Doin & Cie, 1939).

The most extreme degree of degeneration corresponds to the Argyll Robertson phenomenon: complete absence of reaction to light. But it is important to emphasize that before the Argyll Robertson stage is reached there can be detected, pupillographically, a long evolution of seven well defined stages, the first three or four, or even five, of which cannot be detected by the naked eye.

Cases exist, in the preclinical stage of cerebrospinal syphilis, in which both pupils react promptly and fully but in which one finds increased fatigability of one side.

Frequently one finds, as a first symptom of an incipient syphilitic lesion of the brain, that dissociation of consensual and direct reaction which I have called dynamic anisocoria. Dynamic anisocoria may affect either the reaction to light or the reaction to near vision, and both types may occur in acquired syphilis.

Static anisocorias, occurring in cases of sympathetic lesions, are generally not of syphilitic origin.

Pupillographically, these different types exhibit characteristic forms: sympathetically conditioned anisocorias disappear during contraction; parasympathetically conditioned anisocorias develop or increase during contraction. This phenomenon, found in collaboration with Franceschetti, has been called the "law of convergence and divergence of pupillary reactions." Convergence between the traces of the direct and the consensual reaction has generally a nonsyphilitic origin.

Practically, the most significant contributions of pupillography so far lie in its making possible: (1) differentiation between organic and nonorganic lesions; (2) the early diagnosis, and hence prophylaxis, of syphilitic lesions in the central nervous system.

DISCUSSION

DR. J. F. FULTON, New Haven, Conn.: I have been fascinated by Dr. Löwenstein's presentation. I am familiar with his work. I think the opportunity which it affords to observe disturbances in the oculomotor system at a stage which antedates the more profound disturbances in the central nervous system furnishes a tool which must be of great value and have a real future, not only in neurology but, as Dr. Löwenstein modestly pointed out, also in psychiatry. From the physiologic standpoint, I wish to ask him for my own information what is the effect of cortical lesions on pupillary responses. The work is revealing from a physiologic standpoint, since the reflex pathways involved in these reactions are still obscure anatomically as well as physiologically. It was a great pleasure to hear this paper.

DR. MORRIS DAVIDSON (by invitation): I wish to ask whether there are available any pupillograms dealing with intraocular conditions, such as lesions of the macula and iris, apart from posterior synechiae.

DR. BERNARD SACHS: I am happy that Dr. Löwenstein has gone so thoroughly into this work and has substantiated contentions some have made for many years, especially in regard to the value of the pupillary symptoms in neurosyphilis. For years I have attached much more importance to the pupillary reactions in early syphilis than I do to the Wassermann or to any other blood test. I have great confidence in the work Dr. Löwenstein has done, and I hope he will report more about it from time to time.

DR. OTTO LÖWENSTEIN: There are certain pupillographic types which are associated with fundic lesions or other intraocular conditions. I did not mention them because of lack of time. However, ocular conditions must be detected in each case, and collaboration between the ophthalmologist and the neurologist is a sine qua non for pupillographic interpretation.

The question of the relation between the Wassermann and the pupillographic test in the diagnosis of incipient syphilitic lesions of the central nervous system is to be answered as follows: It is generally known that in a certain percentage of cases, such as those of latent syphilis, of syphilitic infections which seem to be arrested and of so-called syphilis without symptoms, pathologic processes of the central nervous system develop, apparently suddenly. In these cases, in which the Wassermann reaction is generally negative, pupillographic findings are often positive at an early stage, enabling one to follow the further development of the disease. One could follow a certain number of cases, disclosed by pupillography, in which the Wassermann reaction, either in the spontaneous course of development of the disease or under the influence of antisyphilitic treatment, becomes positive. The pupillographic test is restricted to lesions of the pupillary paths and their connections. The Wassermann test indicates the existence of a general syphilitic lesion and is practically specific. The pupillographic test is per se nonspecific. However, there are two reasons for the great importance of pupillographic tests for the diagnosis of syphilitic lesions in the central nervous system: (1) the extensiveness of the anatomic structure and its connections; (2) the fact that parts of this structure are loci minoris resistentiae for syphilitic lesions and these lesions are pupillographically well defined according to their localization.

The six stages of pupillographic modifications preceding the real Argyll Robertson phenomenon are characteristic of syphilitic lesions to the same degree as the Argyll Robertson phenomenon itself, that is, in about 98 per cent of cases.

However, the Wassermann and the pupillographic test supplement one another. The pupillographic test should be applied (1) in cases in which the Wassermann reaction is positive, to relate it to particular lesions of the central nervous system, and (2) in cases in which the Wassermann reaction is negative and indefinite and the neurologic or psychologic symptoms point to the presence of an incipient organic lesion of the central nervous system which can be detected in this early stage by the pupillographic test.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

GILBERT HORRAX, M.D., *President, in the Chair*

Regular Meeting, Jan. 18, 1940

Metabolism of the Brain in Insulin Hypoglycemia, as Demonstrated by the Method of Internal Jugular Venous Puncture. DR. JULIUS LOMAN.

In 1935, Dameshek and Myerson demonstrated in man that during insulin hypoglycemia two important changes occur in the metabolism of the brain: first, a decrease in the uptake of sugar and, second, a decrease in the consumption of oxygen. That improvement in dementia praecox following insulin shock therapy is related to a change in either the sugar or the oxygen metabolism of the brain is believed by many investigators. More specifically, it is postulated that following the depression of the sugar and oxygen metabolism which results during insulin hypoglycemia there is stimulation of cerebral metabolism. As Gerard stated, shock therapy directly or indirectly increases the oxidation of sugar, which is the preferred, or probably the only, fuel utilized by the brain. If this theory is correct, one would expect that in the process of recovery from insulin hypoglycemia increased utilization by the brain of sugar or oxygen or both might occur. The present study was carried out to test this theory.

Two groups of subjects with dementia praecox were used in the experiments. In the first set of experiments blood was collected simultaneously from the internal jugular vein, the brachial artery and the basilic vein before, during the height of and at various periods following the insulin hypoglycemia. After the samples of blood were obtained at the height of the insulin reaction, dextrose (100 to 200 Gm. by mouth) was administered. The differences in sugar contents of arterial, internal jugular venous and basilic venous blood of these patients were followed. In the second set of experiments, samples of blood were obtained before, during and after the insulin reaction from the brachial artery and the internal jugular vein, and the sugar and oxygen contents of the samples were determined.

Although the uptake of sugar by the brain was always diminished, decreased consumption of oxygen was not always demonstrated at the height of the insulin reaction. During the period of recovery from the insulin hypoglycemia there was no evidence of an increased uptake of oxygen or sugar by the brain, as measured by the differences between arterial and venous blood. The uptake of sugar continued to be diminished for the duration of the experiments (up to two hours). That the diminished differences in sugar, and sometimes in oxygen, are not due to alteration in blood flow is indicated by the observations made in previous studies by Myerson and me that during the insulin reaction there is a diminished cerebral flow, which would result in an increased difference in the sugar and oxygen contents of arterial and of venous blood. As compared with the uptake of sugar in the brain the uptake in the arm returned to normal levels much more quickly, which indicates that the brain lagged behind the arm in its recovery, as measured by the differences between arterial and venous blood.

So far as these data are concerned, there is no evidence that the sugar or oxygen metabolism of the brain is stimulated after insulin hypoglycemia; therefore, they do not bear out the widely held theory that the improvement in mental disease following insulin shock therapy is related to increased oxidation of sugar by the brain.

DISCUSSION

DR. WILLIAM G. LENNOX: This is a valuable piece of work. However, I wish to question the use of the word "uptake." When there is a decrease in the sugar content of the blood returning from the brain, does it mean that the

metabolism of the brain is increased (an increased difference between the content of arterial and that of venous blood), or may it not mean that the blood is merely passing through the brain more slowly? Does Dr. Loman have any observation on blood flow in the brain during insulin hypoglycemia? The Gibbs flow recorder is hardly dependable for prolonged observations. Some work has been done in Cincinnati with a new method for measuring cerebral blood flow in human subjects which indicates a decrease in cerebral flow during hypoglycemia. These observations, if confirmed, tend to substantiate Dr. Loman's use of the term "uptake."

DR. JULIUS LOMAN: About three or four years ago Dameshek and I, using Dr. Gibbs's recorder, studied cerebral blood flow during insulin hypoglycemia. A slight decrease was found. This indicates that the change in blood flow in insulin hypoglycemia does not account for the diminished uptake of oxygen and sugar by the brain. On the contrary, with a diminished blood flow one would expect an increased rather than a diminished difference in the oxygen and sugar contents of arterial and of venous blood. Therefore, the changes observed in these experiments are best explained on the basis of an actual decrease in the sugar and oxygen metabolism of the brain.

Results of the Total Push Method at the McLean Hospital. DR. KENNETH J. TILLOTSON, Belmont, Mass.

During the past fifteen months, 67 patients have received the activation-motivation and reeducation treatment under the "total push" regimen. These 67 patients fall into three groups, 29 patients who were characterized as having acute schizophrenia having been hospitalized less than two years, or an average of nine and a third months. Of the group with acute schizophrenia, 8 showed slight improvement, 10 marked improvement and 11 good clinical recovery. The remainder of the total number are divided into two groups, designated as patients with chronic schizophrenia. In the first group the patients had been ill for between two and twelve years. The total number in this group was 26, and the average length of hospitalization was six years. Three of these patients showed no improvement, 8 slight improvement, 12 marked improvement and 3 good social and clinical recovery. The third group of patients, who had been ill over twelve years, consisted of a group of 12 patients, whose average length of hospitalization was twenty and four-tenths years; 2 showed no improvement, 4 slight improvement, 5 marked improvement and 1 the equivalent of a social recovery.

Total Push Treatment at Danvers State Hospital. DR. LEO MALETZ, Danvers, Mass.

The total push program was instituted at the Danvers State Hospital about six months ago. A small group of patients who had been in the hospital for at least ten years without having shown any significant remission was selected. The film shown was taken at the beginning of the program of treatment. It demonstrates well the regressive features of schizophrenia. Aversion of the gaze is particularly noticeable. Only 1 patient looked directly at the camera. The withdrawal of these patients is marked. They manifest no interest in the activities of the photographer. They seem indifferent and devoid of emotion. The general appearance of the group is particularly characteristic. They are shabby, unkempt and careless. Their motor movements reveal clumsiness and poor coordination. Unfortunately, I cannot at this time present a comparable film showing the improvement. However, it can be claimed that all the patients have shown some measure of improvement, notably in the field of behavior and outward responses. They have acquired an interest in their appearance and are better groomed; their withdrawal and aversion have diminished. Improvement in verbal production has not been so noticeable. Hallucinatory and delusional trends still persist,

and there is still marked disorganization of thought processes. It has been found that the patients respond well to recreational activities. Competitive sports are much better received than routine exercises. Patients took to ping pong readily and acquired considerable skill and dexterity.

A portion of the cost of the experiment is balanced by the marked diminution in the destructiveness of the patients. Patients who required prolonged seclusion now have ward privileges and have adjusted well. I believe as a result of this program improvement can be effected in cases of schizophrenia of long duration.

More recently, 2 patients have been added to this group who had postencephalitic disorders in behavior. They are intractable and lack inhibition and control. They are subject to frequent episodes of disturbed and impulsive behavior. Both patients have shown considerable improvement.

Total Push Treatment of Chronic Schizophrenia at the Metropolitan State Hospital: Preliminary Report. DR. ELVIN V. SEMRAD and DR. WILLIAM CORWIN, Waltham, Mass.

A report of the total push method in the treatment of chronic schizophrenia is presented in the form of a moving picture to illustrate the type of patients treated and the various activities in which they took part and to summarize improvement in behavior as recorded in the Gardner behavior charts. The duration of the experiment was five months; the report, therefore, must be considered as preliminary. Only objective evidence is presented, and impressions and results on which observations are still incomplete are omitted.

The patients chosen for active treatment were 10 men with disorders diagnosed as schizophrenia; the average age was about 35; they had been hospitalized for an average of fourteen and two-tenths years.

The patients chosen as controls for the experiment were 10 men with disorders diagnosed as schizophrenia; the average age was about 35; they had been hospitalized for an average of twelve years.

Clinically, the patients presented signs of "deterioration," solitude, retreat from organized activity, passivity, mutism, nonsociability, mannerisms and untidiness, with a history of hallucinations and delusions.

The daily schedule of activities followed by the patients during active treatment follows.

Time	Week Days	Sunday and Holidays
6 a. m.:	Arise, hydrotherapy (showers, etc.), dress	
7:15-8 a. m.:	Breakfast	
8-9 a. m.:	Physical therapy—sun baths, ultraviolet ray baths, etc.	Church
9-10 a. m.:	Physical education—calisthenics, gymnasium	
10-11:15 a. m.:	Occupational therapy	
11:15-12 M.:	Dinner	
12-1:30 p. m.:	Rest period	
1:30-2:30 p. m.:	Occupational therapy, e. g., gardening	
2:30-3:30 p. m.:	Physical education—baseball, roller skating, etc.	Church
3:30-3:50 p. m.:	Shower	and
3:50-4:30 p. m.:	Library—current events, etc.	visitors
4:30 p. m.:	Supper	
7-8 p. m.:	Movies, games, dances, radio	

The patients used as controls were allowed to remain in the wards for continuous treatment; they were limited essentially to custodial care; they sat about the ward and took no interest in available organized activity.

Moving pictures of active treatment show patients roller skating, working in the garden and participating in calisthenics, tumbling and physical and occupational therapy. The exercises were graded and adapted to the particular ability

of the individual patient as outlined by Thompson and one of us (W. C.). The various activities demonstrated possible avenues of motor expression enjoyed by the patients. Changes in mental and physical status are not presented at this time. The factors of interpersonal relations of patients and personnel are mentioned, and it is hoped that more detailed reports may be communicated later. The change in behavior as recorded before and after a period of five months of treatment is summarized. One can note general improvement in total average behavior, temper control, appetite, sociability, control of activity, self entertainment, control of combativeness, care of property, appearance and cooperation in routine.

DISCUSSION ON PAPERS BY DRS. TILLOTSON, MALETZ AND SEMRAD AND CORWIN

DR. ABRAHAM MYERSON: I think it will be agreed that the selection of patients was made to exclude any spontaneous improvement. The Danvers group is typical of patients selected from all the hospitals. The cards have been stacked against the experiment as heavily as possible. Any improvement that takes place is 100 per cent gain. As I have observed at the McLean Hospital and at other hospitals, a definite improvement in conduct takes place. The more time and effort that are given to the individual patient the greater the improvement in these cases of chronic schizophrenia. Taking care of the patients more or less superficially in large groups, without individual attention, without individual focusing of praise, blame or punishment, that is, without motivation as well as activation, brings superficial results. Such patients are much better while one is working with them and do not show much improvement at other times.

On the other hand, the individual effort put into the treatment, as at the McLean Hospital, which may be impossible at most hospitals, results in definite improvement in all spheres, including even the psychic inner picture: hallucinations, delusions, thought processes, integration and personality. The return is proportionate to the amount of effort and motivation. It is safe to state that when the total push treatment is carried out on a large scale general improvement is gained without any great advantage, but when specific individual attention is given, patients do remarkably well, considering what they started from. Those of us, such as Dr. Tillotson and I, who are interested in the project have no hopes that this is a cure for schizophrenia. At present there is no such cure. However, when one works with schizophrenic patients one learns about schizophrenia. I can go into a hospital now and pick out in a five minute examination the patients who will do well and those who will do poorly on an activation program. The patient with passivity, but with some cooperation, does well. The patient with a great deal of automatic endogenous activity does not do well.

I can report for the group as a whole and for the hospitals as a whole that an "activation-motivation" program, which is a better descriptive term than "total push," has a markedly beneficial effect in cases of the chronic form. The effect it has on the acute form is less easily ascertained, largely because patients with acute conditions recover spontaneously and the percentage of recovery is unknown.

DR. WILLIAM G. LENNOX: What is the effect of the total push method on those who give this treatment? Has there been an increase in breakdown from overwork among them, or have the hospitals had to increase their staffs?

DR. ABRAHAM MYERSON: The most beneficial effect of the total push method has been on the hospital staff. They have passed from apathy, somnolence and retreat into normality. They have moved from an attitude of defeatism and "lying down" characteristic of psychiatry in the past, to that of general alertness taken by modern psychiatry, regardless of what they may be doing to the race as a whole. The business of a physician is to cure the sick and to proceed actively in that program. The improvement of the hospital staff is the most important fact resulting from this treatment of schizophrenia.

Results of Treatment of Epilepsy at Grafton State Hospital. Dr. Benjamin Cohen, Dr. Nathaniel Showstack and Dr. Abraham Myerson.

This paper was published in a recent issue of *The Journal of the American Medical Association* (Synergism of Phenobarbital, Dilantin Sodium and Other Drugs in the Treatment of Institutional Epilepsy, *J. A. M. A.* **114**:480-484 [Feb. 10] 1940).

DISCUSSION

Dr. H. Houston Merritt: Dr. Cohen is to be congratulated on this study. It shows what can be done with epileptic patients when they are intelligently treated. A defeatist attitude in the treatment of epilepsy has been taken in the past, and physicians have eased their consciences by prescribing ½ or ¾ grain (0.032 or 0.049 Gm.) of phenobarbital. An adequate dose is rarely given. Dr. Cohen has shown what such a dose will do for patients. An adequate dose is rarely less than 1½ grains (0.097 Gm.), and is often over 2 or 3 grains (0.13 or 0.195 Gm.). Dr. Cohen has shown that treatment with phenobarbital is the simplest and most efficient method known. In the experience of my associates and myself, use of dilantin sodium was confined for experimental reasons to patients who failed to be helped by phenobarbital. Not infrequently patients will be benefited for from six months to two years by phenobarbital, and then no matter how high the dose is pushed they no longer respond. Most of our patients were of this type. No doubt many patients started on treatment with dilantin sodium may become refractory to it and can then be shifted back to phenobarbital again. Dr. Cohen has ably shown the benefit from the synergistic use of these drugs. Dilantin sodium can be added to phenobarbital without any added hypnotic effect, and the anticonvulsive effect can be raised. He has shown also that the anticonvulsive action of phenobarbital is not due to its hypnotic effect. The patients can be kept awake by benzedrine and still the anticonvulsive action of the phenobarbital is manifested. This means that there must be some specific anticonvulsive drug which is entirely devoid of any hypnotic action, and some day it may be found.

The changes in the gums which were spoken of have no relation to vitamin C. Patients in the outpatient department, and probably those in hospitals for chronic disease, usually have a diet low in vitamin C. A study of a group of these patients has shown a low vitamin C level in the blood, regardless of whether they were receiving medication, i. e., dilantin, or not. If they are given a full vitamin C diet the vitamin C level will rise.

Dr. Julius Loman: What are the comparative figures on the effectiveness of these drugs in treatment of petit mal and of grand mal?

Dr. Benjamin Cohen: We made no statistical distinction between petit mal and grand mal seizures, but recorded only changes in the total number of seizures. This was done because our records of seizure expectancy per patient were based on undifferentiated seizure aggregates, and because ward attendants do not separate consistently the two types of attacks. In our experience, seizures were predominantly grand mal at the start of our program. As treatment progressed, both the incidence and the severity of seizures diminished. In many cases residual attacks changed from the grand mal type to forms intermediate between grand mal and petit mal.

Dr. Kenneth J. Tillotson, Belmont, Mass.: Can Dr. Lennox say how drugs affect the electroencephalogram between attacks?

Dr. William G. Lennox: I wish first to say something on my own account. I think one would not realize the excellency of this paper if one did not know how little has been written on the comparative results of various drugs in the treatment of epilepsy on the basis of an actual count of the number of seizures. This is really a valuable interpretation.

I am disappointed that Dr. Merritt did not explain why Dr. Cohen's patients reacted better with phenobarbital alone than with dilantin alone. It occurred to me that Dr. Loman's question might answer it, in that the attacks in many of

the cases may have been of the petit mal type, which is occasionally made worse by dilantin.

Dr. Merritt, Dr. Gibbs and I have been studying the effect of the various drugs on the electroencephalogram. The improvement in seizures and the improvement in the electroencephalograms do not parallel each other. Patients may have freedom from attacks while taking dilantin, and yet their electroencephalographic record may be as bad as ever. On the other hand, they may be free from attacks but the record be much better. Probably the electroencephalographic record will prove a surer method of determining the effect of various medications than is the count of the number of seizures. We have not done much with the effects of the various drugs on the electroencephalogram, but we do know that the problem is complicated by the type of seizure under consideration. To me the most striking thing is the benefit which the patient having so-called psychomotor seizures obtains with dilantin sodium as compared with the negligible effect he secures with phenobarbital or bromides. Therefore, I think this study needs to be broken up so that different types of seizures are dealt with.

Dr. Abraham Myerson: I have been associated with this research since the beginning and have carried it out in my own practice. Generally speaking, it seems to me that phenobarbital and dilantin should be used from the first if one has in mind not so much the electroencephalographic record as the symptoms, that is, convulsive or petit mal attacks. The two drugs work remarkably well together, and seizures are greatly reduced. One now has the feeling that one can do something of importance. One can greatly reduce, diminish and even entirely abolish seizures by careful study of the number of attacks and the individualization of the dose.

Dr. Putnam and Dr. Merritt deserve a great deal of credit because they pointed out that the sedative effect was not necessary, that a phenyl compound was essential for the antiepileptic effect. There are available, therefore, phenobarbital, dilantin sodium and mebaral—a phenyl derivative, methylethylphenyl barbituric acid—and a drug also having little sedative action. One has a series of drugs characterized by one general constituent, i. e., a barbiturate or a similar combination, such as hydantoin, associated with a phenyl radical. Mebaral seems to be worthy of much more attention than it receives. This drug, combined with dilantin, is the treatment of choice. Mebaral is fully as effective as phenobarbital. It lacks sedative, narcotic action, and it has no toxic effect. Drowsiness, which appears occasionally, is easily dissipated either by caffeine or by benzedrine. This enormously reduces seizures. One can now promise relief to patients with petit mal or grand mal from the combination of mebaral, 6 grains (0.39 Gm.) a day, and dilantin sodium, 3 to 4½ grains (0.195 to 0.292 Gm.) a day. The effect is a revelation so far as the treatent of epilepsy is concerned.

This is another instance of the prevalence of a good scientific method over the defeatist attitude characteristic of psychiatry in the past. I think psychiatry is entering an era of nondefeatism.

Dr. Benjamin Cohen: I wish to add a statement concerning the expected incidence of seizures and the recognition of effective medicinal agents in the treatment of epilepsy. Under unchanged circumstances or when drugs are used which do not affect seizure incidence clinically, such as prostigmine, dextrose, insulin, caffeine and benzedrine sulfate, groups of epileptic patients show scant change in their total number of seizures per ten or more weeks. However, improved medication, such as the addition of dilantin sodium to the medication of patients who are receiving no further benefits from increases of phenobarbital, results in an early proportionate decrease of seizures, which tends to be maintained approximately through succeeding months. Similar benefits are brought about by the addition of bromides. If an effective antiepileptic medicine is discontinued, succeeded by an ineffective agent, or replaced by an inadequate amount of an equally effective agent, seizures tend to increase. The maintenance of benefit when other effective medication is replaced by mebaral in adequate quantity offers proof of its value.

BRONSON CROTHERS, M.D., *Presiding*

Regular Meeting, Feb. 15, 1940

Frontal Lobotomy in Two Patients with Agitated Depression: Therapeutic Evaluation and Further Reference to Function of the Frontal Lobes. DR. W. J. MIXTER, DR. K. J. TILLOTSON, Belmont, Mass., and DR. D. DAVID WIES, Belmont, Mass.

Two cases of agitated depression treated by "prefrontal lobotomy" are reported, the first of such operations in New England, and the first in which electroencephalographic studies have been made preoperatively and postoperatively. The surgical aspects are discussed by Dr. William Jason Mixter and clinical and psychometric examinations by Drs. Tillotson and Wies of the McLean Hospital. In both cases there was depression with "rut" formation; in addition, in 1 case operation revealed possible Alzheimer's disease, and in the other cortical atrophy, possibly related to presenile changes or trauma, was shown before operation.

REPORT OF CASES

CASE 1.—A man aged 67, with no positive hereditary features, had been a quiet, passive, asocial person all his life, without interests and with fitful performance at school and in business; he always "talked a good game," put on a grand manner and was aloof and fastidious. After the World War he was unable to reestablish himself, drank heavily and took sedative drugs. In 1928 he became depressed and suicidal, with development of hostility toward his family. On admission to the McLean Hospital in 1936, he was in a panicky, depressed state, agitated, suspicious and stereotyped in behavior. He then went to a ranch and to Brattleboro Retreat, without improvement. He was readmitted to the McLean Hospital in 1937. Mental tests, although the results were unsatisfactory, showed no definite intellectual impairment.

In March 1938 frontal lobotomy was performed at the Massachusetts General Hospital. He became quieter, talked more normally and had only mild return of fear and suspicions at times. Postoperative tests showed no intellectual or physical changes, although he was slower and less alert. He was discharged from the hospital eighteen months ago. He refused to return for a check-up. His family reports that agitation and paranoid trends have disappeared, at least on the surface. He has renewed acquaintances, takes no alcohol or drugs and is interested in religious matters. He lacks energy and initiative, but is more normal than for years.

CASE 2.—A man aged 55 was admitted in 1932 with a diagnosis of manic-depressive depression. One daughter was mentally retarded; his wife was mentally ill. The patient was a respected, religious, sociable person until he had business reverses in the twenties. He attempted suicide and was brought to the McLean Hospital. He was agitated, suicidal and depressed, and nearly inaccessible. In 1934 there developed a shuffling gait, jargonaphasia and smacking of the lips. He became less suicidal, played golf and read, but was not communicative with the hospital staff. In July 1938 there developed a duodenal ulcer, which was treated successfully. Later, electroencephalograms showed abnormal activity in the brain, and a pneumoencephalogram showed cortical atrophy. Neurologic examination gave unsatisfactory results.

After a stormy course following an operation in February 1939, the patient recovered during a period of months. Agitation nearly disappeared, as did the abnormality of speech, gait and posture. Under the "total push" regimen he became active in hospital activities. He became more friendly, although he was passive and did not show much warmth of feeling. From an open ward he made visits to the country, and was discharged "on visit" in August 1939.

Postoperative Otis and army alpha tests showed an intelligence quotient of 91 to 93, with difficulties in the more synthetic functions but no disturbances in memory. Those losses may have been due to presenile changes rather than to the operation. Rorschach tests at the hospital and in January 1940 showed an unremitting picture of depression, mental torpidity and lack of drive, with an even duller

picture at the time of the second test. There appeared to be evidence of organic damage as well as depression.

Clinically the patient presented a depressive mental outlook, with apathy. Neurologic and physical examination revealed moderate hypertensive sclerotic changes and absence of vibration sense in the lower extremities. No signs of damage to the frontal lobes were revealed by neurologic examination. The patient shows little initiative and interest, but manages his small needs at home now without attendance. The results are startling in view of the extreme hopelessness in his case.

We believe that frontal lobotomy may be of value in cases of long-standing agitated depression, even if complicated by mild presenile changes or alcoholism, when the prognosis is grave. Further, we recommend the "total push" regimen for reactivation in convalescence. The psychosis is not "cured," but an affective "deafferentation" seems to take place which lessens hypermotility and abnormal concern. The effects appear to be lasting.

The Electroencephalogram (Dr. Pauline A. Davis).—In October and November 1936, electroencephalograms of both patients were taken. Records were made from midline placements on the frontal, precentral and occipital areas. More complete encephalographic studies of the first patient were made four months before operation, in that besides midline placements corresponding areas on both the left and the right side of the head were included. Little difference could be observed in the activity of the various areas, and there was no asymmetry between the left and the right side. A postoperative electroencephalogram was later recorded from the same placements. Thorough analysis of all three records showed little if any change. The patient's behavior appeared to be fundamentally unchanged in the laboratory before and after the lobotomy.

The second patient has had five electroencephalograms, the first being recorded in November 1936. In November 1938, two years later, two much more complete studies were made, which included the frontal, precentral, temporal, parietal and occipital areas on the left and the right side. The activity from all leads represented the same generalized overactivity that had been seen in 1936, but was greatly exaggerated, disorganized and continuous. In addition, there were episodes of high voltage appearing on the left from the parietal area to the occipital and to the precentral region. None of these episodes occurred on the right side of the head. This high voltage activity was localized, while at the same time a profound physiologic storm continued to disturb the entire brain. At this time a continuous jargon of speech and excessive motor behavior were beyond the patient's control. Nearly three months after these records were taken, on Feb. 2, 1939, lobotomy was performed. A fourth electroencephalogram was recorded on March 20, 1939, about seven weeks after the lobotomy. Only careful observation at this time made it possible to detect the behavior pattern he had previously manifested. The electroencephalogram showed no change in its fundamental original characteristics of alpha frequency and voltage, but the superimposed abnormality, which was evidence of profound and continuous physiologic disturbance, was greatly reduced and the record was entirely free from episodic activity. The improvement in the electroencephalogram corresponded perfectly with the improvement in the patient's behavior. A fifth electroencephalogram, taken eleven months after operation, showed a further change toward greater stability in the pattern and a marked decrease in the continuous abnormal activity that was still present in the first postoperative record, interfering with the fundamental pattern. Comparison of all five electroencephalograms taken from 1936 to 1940 reveals that the alpha frequency is still 10, of the same voltage, responding in the same manner to opening and closing the eyes and maintaining a normal wave form. These are the fundamental and characteristic factors of this patient's electroencephalogram.

The records from the 2 patients were made in the same manner, and similar lobotomies were performed. The patients differed in that one (case 2) was suffering from a localized intermittent disturbance involving the left side of his head. The profound physiologic overactivity involved speech and the motor

areas. The pneumoencephalogram revealed left hemiatrophy. Furthermore, the activity of the other areas was continuously abnormal, generalized and consistent. The lobotomy, by cutting the tracts subcortically without disturbing the cortex, relieved the patient of this profound overactivity.

Interpretation: The effect of the lobotomy on the electroencephalogram in case 2 appears from the data to show that characteristic, physiologic activity of the cortex is not impaired by undercutting. The tracts connecting one part of the cortex to another have been severed. This implies that there is less opportunity for the incoming stimuli to affect the brain so much. In this case the frontal lobes are just as closely adjacent to the premotor and motor areas as they were before. The pathways connecting these areas with one another and the frontal cortex with subcortical regions have been severed. Therefore the cortical areas should act more closely together and in unison, since incoming stimuli no longer play on them. When one compares the preoperative and the postoperative electroencephalograms, one sees that the same elements, both normal and abnormal, are there. The areas are behaving in their characteristic manner. Wherever the pacemakers reside in the brain, they can no longer modify the profound overactivity or distortion of activity in one part of the brain. The other part of the brain seems to maintain more consistent activity. There are much greater similarity and reduced differentiation of the frontal, precentral, parietal and occipital areas postoperatively than preoperatively. The particular parts of the cortex are not so specifically modified by incoming impulses, because these impulses do not reach the cortex by their accustomed pathways. The cells of the cortex can go their own way in peace, without too much disturbance. The person's behavior is probably less specialized than before. What I understand to be characteristic of the cases of lobotomy already reported is that the patients, although aware of the troubles of the world, are no longer bothered by them. In this case a very sick man has been relieved of overstimulation and violent upsets in his brain, and this has given him new life and a chance to leave the hospital and live in the more normal surroundings of the world.

DISCUSSION

DR. IVES HENDRICK: I wish to ask for a clarification of one remark, that recommending frontal lobotomies in all cases of agitated depression. If not in all, then in which cases is it recommended and how are these differentiated? I wish also to ask whether this method might be applied in other cases of hopeless psychoses.

DR. KENNETH TILLOTSON, Belmont, Mass.: If this type of operation were recommended in all cases of agitated depression we should be criticized severely. These cases were instances of prolonged agitated depression in which the patients were going downhill and in which all modes of therapy had been tried or contemplated. The patients had been ill for eight or ten years. In the second case there was nothing to lose, and possibly something to gain. I think it will be agreed that this operation should not be considered in cases of early agitated depression. Psychotherapy, ordinary hospital treatment and institutional therapy, as well as all other means of treatment, should be tried first.

DR. LEO ALEXANDER: It is interesting to look at this problem from the neuropathologic point of view. There are available, as Dr. Tillotson has pointed out, several fundamentally new types of treatment. There is no doubt that insulin, metrazol and frontal lobotomy have been successful in treatment of this condition. Dr. Cobb, in interpreting the successes with the insulin and metrazol treatment, early called attention to the possibility that they may be due to destruction of brain tissue.

Clinicopathologic evidence gradually accumulating confirms Dr. Cobb's original impression. I have had an opportunity to study a case of insulin shock in which there was widespread ischemic degeneration of the cortex, predominantly in the centroparietal region. Dr. Zimmerman, in a paper presented before the New England Pathological Society last year (Lesions of the Nervous System in Hyperinsulinism, ARCH. PATH. **28**:276 [Aug.] 1939), pointed out certain specific features

of this widespread degeneration and necrosis of the cortex which differentiate these "aglycemic" lesions from the anoxic type. Dr. Zimmerman's paper was extremely interesting in view of the fact that he correlated his work with certain psychologic findings obtained in clinical cases of schizophrenia after insulin treatment. Electroencephalographic evidence obtained by Dr. Pauline Davis is equally clearcut in proving organic damage to the brain following metrazol shock treatment.

There is agreement that the clinical improvement following metrazol or insulin therapy is essentially due to destruction of brain tissue, and that the clinical improvement caused by metrazol or insulin treatment has essentially the same rationale as frontal lobotomy. There can be no doubt, from the scientific point of view, that a method in which one knows what parts of the brain are destroyed is preferable to one in which destruction is unpredictable, at random and more or less left to chance.

The method of frontal lobotomy is based on sound clinicopathologic observations dating back as far as 1888, when Welt published the report of her famous case of injury to the orbital lobe. This observation, confirmed by a large series of cases, which has been well reviewed by Kleist, demonstrates that the personality defect caused by injury to the orbital lobe, with its brazen criminality, inconsiderate overactivity and lack of concern about decency, convention and morality, can best be characterized as due to loss of that which psychoanalysts call the "superego," and which Kleist has termed the social ego. There is no doubt that in involutional depressions the superego is overactive, and thereby the destruction of the frontal lobes, including their orbital portion, has a sound basis in clinicopathologic experience.

In a demonstration given by Dr. Freeman in Boston a year ago the orbital white matter appeared to be injured in most of his cases in which lobotomy was successful. I wonder whether it would be worth while to narrow the field of operation still more and investigate whether destruction of the orbital fibers alone would accomplish this result.

Dr. Alexandra Adler: I wish to ask whether all other forms of treatment were tried with these patients before operation, and whether metrazol was given. I think that metrazol ought to be used first. I am interested to see whether lobotomy would help when metrazol does not.

Dr. Kenneth Tillotson: In both cases treatment with metrazol was considered. The patient in case 1 refused metrazol treatment, and the patient in case 2 had a pathologic heart condition so that we did not dare to give metrazol; the electrocardiogram contraindicated this treatment. I agree that there should be a comparable metrazol series of cases. It would be interesting to have such a study.

Dr. David Wies, Waverly, Mass.: In the case of metrazol the improvement seems to be immediate and is followed by relapse. In cases in which the frontal lobotomy is performed improvement is slow and tends to remain permanent in the cases in which it is successful.

Dr. William Jason Mixter: I wish to thank Dr. Alexander for his discussion of lobotomy. It seems to me that as one learns more about the frontal lobe one may be able to secure the desired result without as extensive a section as I have done in these 2 cases. We are progressing slowly in this matter in Boston, and I think that is wise. Dr. Freeman and Dr. Watts have had a great deal of experience, and it is desirable that they should lead the way. So far, we have selected cases of agitated depression and have not tried this operation in any other group. The question of cortical excision instead of section of the tract has been raised. It is probable that cortical excision would be more likely to cause epilepsy than section of the tract, because of the increased amount of cortical scar. For this reason I am not in favor of cortical excision at present.

Suicide as Wish Fulfillment. Dr. Ives Hendrick.

This paper was published in full in the January 1940 issue of the *Psychiatric Quarterly*, page 30.

Book Reviews

Contributions from the Research and Neuropsychiatric Gannushkin Institute. Part 1. Edited by S. V. Kraiz and M. Z. Kaplinsky. Price, 11 rubles, 50 kopeks. Pp., 412. Moscow, U. S. S. R., 1936. Part 2. Edited by M. Z. Kaplinsky, S. V. Kraiz (Chief Editor) and M. J. Sereysky. Price 9 rubles. Pp. 236. Moscow, U. S. S. R., 1938. Part 3. Edited by T. A. Geyer, S. G. Jislin, M. Z. Kaplinsky, S. V. Kraiz, A. S. Kronfeld, M. J. Sereysky, P. E. Snessarew and A. V. Snejnewsky. Price 14 rubles. Pp., 311. Moscow, U. S. S. R., 1939.

With the exception of a dozen articles, the fifty contributions making up the three volumes deal with schizophrenia—its history, symptomatology, differential diagnosis, complications by other diseases, course, chemistry, serology, pathology and treatment. The history of schizophrenia is extensively reviewed by Kronfeld (in two articles, of 100 pages). Kronfeld is of the opinion that schizophrenia is an organic disease, which may occur in an attenuated form (schizophrenia mitis); it is not associated with intellectual decay; it exhibits only mild personality changes, and the patient's contact with the outside world is not affected. The majority of articles are case reports, many being accompanied by extensive discussions of theoretic, or rather hypothetic, character, but are interesting, as the detailed histories give a picture of various phases of life (personal, family and social) of a Soviet citizen. The treatment of schizophrenia is covered in great detail, "insulin therapy" being the method most extensively discussed. The entire second volume is devoted to a discussion of the treatment of schizophrenia with insulin. Complete remissions were obtained in 31.5 per cent of cases; the prognosis was fairly good for acute schizophrenia, and was worst for hebephrenia.

Three articles deal with the pathologic characteristics: one with Virchow-Robin spaces (in "normal" and "pathologic" conditions), and two with the microglial reaction in senile dementia and schizophrenia.

The interesting conclusion is drawn that schizophrenia is a toxic encephalopathy in which, in addition to areas of devastation (avascular and acellular), there are regressive changes in the glia (ameboid glia cells and clasmatodendrosis) and absence of microglial reaction. When a toxic encephalopathy exhibits microglial reaction it is not schizophrenia.

Pathophysiologic Problems and Treatment of Schizophrenia. Prof. V. P. Protopopov, editor. Contributions from the Central Psychoneurologic Institute. Price, 10 rubles. Pp. 208. Kharkov, U. S. S. R., 1938.

This volume contains fifteen articles, all dealing with problems pertaining to schizophrenia. The authors emphasize that as schizophrenia is not an anatomic disease and has been studied mainly by psychologic methods, the application of the physiologic principles of the school of Pavlov may be of value. Pavlov defined schizophrenia as a chronic hypnotic state, which involves both the cortical and the subcortical fields and serves as a protective inhibitory mechanism of "varied intensity and extensity." In schizophrenia the conditioned and nonconditioned reflexes are diminished, or are obtained with difficulty; they easily disappear and generally indicate lowered tonus of irritability of the cortex and the subcortex. There is a disturbance in balance between the irritability and the inhibition of the ganglion cells, the function of the cortical cells being on the whole markedly reduced.

A number of articles, on such subjects as platysmographic observations in cases of schizophrenia, the phytotoxic reaction (which disclosed retardation of growth of the white lupine in the blood serum of schizophrenic patients, and which indicates the presence of a toxin) and the response of patients to electric currents of various strengths, seem to sustain the opinion that in schizophrenia the function of the ganglion cells is inhibited. Protopopov, the editor of this volume, calls the condition protective inhibition. Intravenous injections of caffeine and bromides gave good results in treatment. Methods of therapy, such as administration of sulfur in liquid petrolatum, which was used alternately with intravenous injections of potassium permanganate, and prolonged sleep, are discussed. The contributions, especially those dealing with the physiologic problems, are of unquestionable interest. They are well abstracted, all in French.

The Content of Cells and Proteins in the Normal Cerebrospinal Fluid. By A. V. Neel. Price, 7s 6d. Pp. 142. London: Oxford University Press, 1939.

The author attempts to determine, from a critical examination of the literature and the results of his own extensive experience, what is the normal content of the cerebrospinal fluid in cells and protein, which he considers the two most important constituents, since increase in protein may result in purely secondary alterations in the electrolytes. Neel prefers the Fuchs-Rosenthal counting chamber, but believes it often advisable to have one with a larger capacity. For determination of the total protein he uses Bisgaard's technic for the Roberts-Stalnikov-Brandberg method, and for globulin, the Bisgaard modification of the Ross-Jones method. For the former method he claims an exactitude of 2.7 per cent when the quantity of protein is small; for larger quantities the Kjeldahl method must be used. Neel claims also that when the two methods are used it is possible usually to dispense with the Lange and similar colloidal reactions. He criticizes former studies because of the nature of the cases utilized. From his own material, including a large number of specimens of fluids removed in producing spinal anesthesia, he concludes that the limits for normal spinal fluid are: globulin, 0; total protein, 13 to 26 mg. per hundred cubic centimeters, and cells, less than 1 per cubic millimeter.

The technic of the tests used is given in detail. The book is clearly and logically written in excellent English.

Problems of Motor Activity in Neurology and Psychiatry. A. I. Heymanovich, Professor Emeritus, State Medical Editor. Contributions from the Central Psychoneurologic Institute, vol. 8. Price, 7 rubles, 50 kopecks. Pp. 209. Kharkov, U. S. S. R., 1937.

The physiologic and pathologic manifestations of motor activity have been studied by a number of Russian physiologists, who have presented their conclusions in twenty-four original contributions, comprising the present volume. The variety of the subjects investigated is great. Some articles deal with comparatively simple problems, such as the facial expression of a schizophrenic person, while others deal with more complex subjects, such as the effect of longitudinal section of the corpus callosum on locomotion, the influence of the cortex on peripheral nerve regeneration or bioelectric currents of the cortex and the causes of their variability in various areas of the cortex. Unfortunately, many articles are unnecessarily verbose (for instance, one, entitled "Central Motor Disturbances and Psychic States," comprises 37 pages in small print), while others are mere abstracts by the authors. It is obvious that a review, however detailed, of such a collective work would do little justice to the authors, and for this reason the originals should be read. Fortunately, the appended abstracts, in English and French, of practically every contribution give a fairly good conception of the subject discussed.

Selected Writings of Sir Charles Sherrington. Compiled and edited by D. Denny-Brown. Price, $7.50. Pp. 532, with 85 illustrations. New York: Paul B. Hoeber, Inc., 1940.

This book is one of the most important publications in the field of physiology and neurology. The editor, Denny-Brown, was a close collaborator of Sherrington and coauthor of Sherrington's book on the "Reflex Activity of the Spinal Cord." He has not merely compiled the numerous papers of Sherrington and presented them in chronologic order, but has carefully selected papers, or even parts of papers, of particular importance for certain problems. This procedure allowed him to give a systematic survey of Sherrington's work on the physiology of the central nervous system and to show the major steps in the development of those problems to which Sherrington devoted his life's work. Short notes of the editor at the beginning of each chapter, and frequently also at the beginning of an individual paper, contain interesting historical remarks or give a brief summary of the content of the paper, thereby facilitating understanding of the problem.

The first three chapters are concerned with the distribution of motor and sensory nerve roots and the function of proprioceptive fibers in muscles. The fourth to the eighth chapter deal with various aspects of reflex physiology, such as spinal shock, reciprocal innervation and postural reflexes. In the ninth chapter Sherrington's famous experiments on the motor area of the cortex are reported, and the last two chapters are concerned with a discussion of the more intimate mechanisms underlying excitatory and inhibitory processes and with the gradation of the reflex response. The book ends with a short passage from Sherrington's "Rede Lecture" on the brain and its mechanism. A complete bibliography is appended. The printing is excellent.

Injuries of the Nervous System Including Poisoning. By Otto Marburg and Max Helfand. Price, $3. Pp. 188, with 16 illustrations. New York: Veritas Press, 1939.

This is probably the worst written book on injuries of the head that has come to the attention of the reviewer. It is so bad, in fact, that much of the worthwhile material is lost on the reader, who resents the murdering of the King's English and whose attention is arrested by strange constructions and misuse of words. Another defect in the work arises from the conflict between completeness and condensation. Many authors are cited, but their theories regarding mechanisms are merely stated, the authors not taking any definite stand or apparently even endeavoring to clarify the matter for the reader. There are even some mislabeled illustrations. The preface contains a lame excuse: "We know that this is a framework, but we quoted the literature to enable the student to easily make up the deficiency." Seventeen pages of recent literature in six languages will not, in the reviewer's opinion, simplify the task of the student of injuries of the head.